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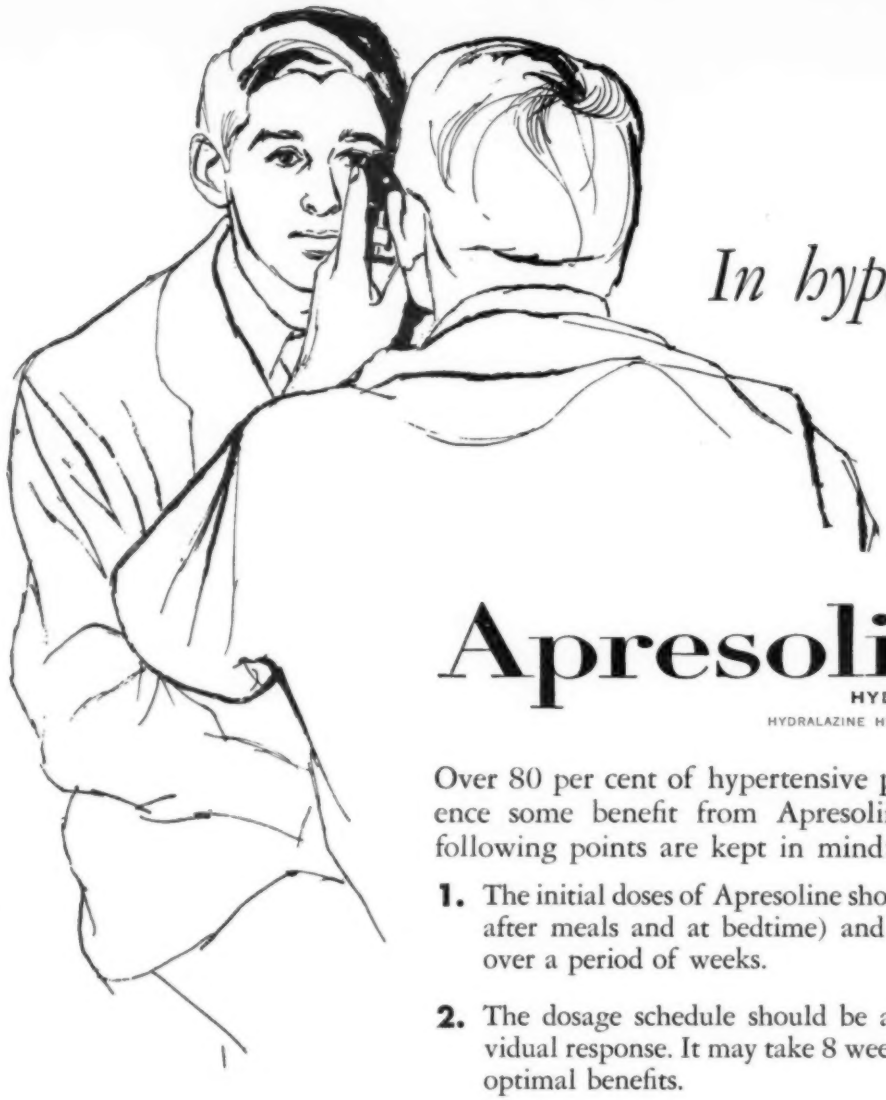

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EVALUATION OF PRESENT DAY TREATMENT OF PEPTIC ULCER

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The treatment of peptic ulcer is an ever increasing problem to the internist and surgeon alike. Those who attempt to treat the ulcer patient conscientiously are daily confused by the multiplicity of articles and conflicting results found in the literature today. There are many advocates of a strict antacid and dietary regimen and almost as many others claim that antacids and diet are valueless. Many substances have been proposed as sure cures for the peptic ulcer patient, only to have this claim upset by reports indicating that placebos are just as effective.

It is extremely difficult for the average busy practitioner to weigh the evidence and sift the facts in an attempt to determine what actually constitutes the most adequate present day method of therapy. It is the purpose of this paper to summarize and clarify the modern treatment of peptic ulcer.

In 1828 Abercrombie (1) first introduced the use of milk, farinaceous foods and lime water in the treatment of this disease. Johnson (2) just three years later introduced the use of soda, magnesia and chalk. In 1835 Cruveilhier (3) emphasized the use of good dietary hygiene and in 1872 Fox (4) stressed the importance of rest. Since that time the treatment of peptic ulcer has been modified very little. The basis for the modern day treatment of peptic ulcer was established by the year 1872; only antispasmodics, sedatives, and psychotherapy have been added.

The etiology of peptic ulcer remains almost as obscure as it was in 1872. No single etiologic factor has been found but many factors have been presented as playing a role in the causation of this disease. Decreased tissue resistance secondary to the loss of the normal mucous barrier has been advanced by some authors as the basic cause of peptic ulceration. No good evidence has appeared to show a decrease in mucin content and the use of gastric mucin in the treatment of peptic ulcer has been discouraging. Other investigators have postulated the presence of gastric atrophy as the cause of decreased tissue resistance and

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ulcer formation. This notion has been discarded, since direct examination of the stomach by means of the gastroscope has failed to show the presence of either chronic gastritis or gastric atrophy in the majority of patients with either duodenal or gastric ulcer. The old concept that either vascular thrombosis or embolism produces an infarction has long been discarded. Other theories as to etiology have included infection, allergy, nutritional deficiency and heredity. None of these theories has withstood the test of time and in no instance has unimpeachable evidence been presented to substantiate these claims. Other factors, such as increased pepsin content, decreased alkaline secretions (pancreatic juice or bile) or decreased secretion of alkaline juice by Brunner's glands, have been incriminated. Studies by Ihre (5), Comfort and Osterberg (6), and Boyden and Berman (7) have failed to demonstrate significant alteration in the rate of secretion of these substances in patients with peptic ulcer.

Intensive survey of the literature indicates that the only consistent finding in the presence of benign peptic ulcer is free hydrochloric acid. Ulcers in the duodenal bulb are usually accompanied by hypersecretion, whereas gastric ulcers seem to be more consistently associated with a normal or low gastric acidity. There seems to be a better case for the presence of decreased tissue resistance in gastric ulcer than in duodenal ulcer. Exactly what this decreased tissue resistance can be attributed to is not, as yet, known. The role of free hydrochloric acid in the production of peptic ulcer is supported by overwhelming experimental and clinical evidence. Experimentally it has been shown that gastric juice containing free hydrochloric acid can digest all living tissues. Ulcers can be regularly produced in animals by stimulating acid secretion by various means. Clinically it has long been known that peptic ulcers develop only in those areas of the gastrointestinal tract exposed to acid gastric juice. These areas include the lower esophagus, stomach, duodenum (first portion), and the jejunum in patients with gastroenterostomies. Ulcers may occur in a Meckel's diverticulum if it contains acid-secreting gastric mucosa. There have been no proven cases of chronic benign peptic ulcer occurring in patients with persistent achlorhydria. Neither Sturgis (8) nor Washburn and Rozendaahl (9) have been able to find a case of benign peptic ulcer in patients with pernicious anemia.

It must, therefore, be concluded that peptic ulcer develops only in patients with parietal cells capable of secreting free hydrochloric acid. The fact that hypersecretion is not found in all patients with peptic ulcer suggests an additional factor, such as decreased tissue resistance, playing a part in the formation of the ulcer. Since the nature of this decreased resistance is not definitely established, the modern treatment of peptic ulcer must be directed at the control of acidity.

The source of hydrochloric acid, the parietal cell, is susceptible to stimulation by many different means. Unfortunately these cells are not as susceptible to depression as they are to excitation. There are, however, many methods available for the neutralization of the acid after it has been produced. That there is no consistent and sure method for this neutralization is manifested by the multiplicty of antacids and dietary regimens prescribed for this purpose. We shall

consider these various methods for controlling free hydrochloric acid and from this arrive at an acceptable program for the treatment of peptic ulcer.

For the past few decades emotional factors have been known to enter into the picture of peptic ulcer. In 1932 Draper and Touraine (10), writing on the man-environment unit and peptic ulcer, felt that "excessive anxiety from the threat of an excessive feminine component in the personalities of men plays a major role in the etiology of peptic ulcer." Since that time various investigators, including Alexander (11), Mittelman and Wolff (12), Sasz *et al.* (13), and others, have reported on the role of emotions in the ulcer patient. That these patients have, in general, an ambitious conscientious type of personality is well recognized by the medical profession in general. Objective evidence of the role of emotions in controlling the gastric secretory rate and motility can be obtained by direct measurements. Since the experiments of Pavlov, numerous investigations have confirmed his contention that gastric secretion in man is predominantly under neural control. That this control is mediated primarily through the autonomic nervous system is borne out by the increased secretion following vagal stimulation. Likewise, decreased secretion has been noted following sympathetic stimulation. The autonomic nervous system activity seems to be concerned only with the regulation of hypersecretory states, and has little to do with basal and nocturnal secretion. Vagal denervation, therefore, usually results in a reduction of the hyperacidity but has relatively little affect on the basal and nocturnal secretory rate. That emotional states play some role cannot be denied. That the emotional-conflict state is the cause of ulcer production is open to serious question. Although it is true that there seems to be a general personality pattern in ulcer patients, there are a large number who fall outside this pattern. It should also be remembered that, although hypersecretion can be induced by certain emotional states, this hypersecretion is of relatively short duration, whereas in most ulcer patients the hypersecretion continues and is most noticeable in the basal and nocturnal secretory rates.

Psychotherapy

There is no proof that psychotherapy of itself, produces material benefit for any substantial period of time. Stine and Ivy (14) have recently reviewed the results of psychiatric therapy in ulcer patients. After sending questionnaires to all members of the American Psychoanalytic Association they were able to collect only 7 cases suitable for follow-up. Of these cases, 2 were reported to be unimproved and 5 improved. The 5 improved patients had been followed for periods of six months to eight years. Three of these were said to have recurrent episodes of substernal and epigastric distress ascribed to "heart-burn," 1 had recurrent episodes of bleeding, and 1 had recurrence of epigastric pain which was felt to be due to ulcer activity. Keeping in mind that ulcers have a proclivity for healing themselves, it would seem that these results cannot be interpreted as being satisfactory. Until further proof of the value of intensive psychotherapy is offered it would seem best that these patients be treated by the internist or family physician. "Superficial" psychotherapy consisting of an understanding

and sympathetic attitude plus a liberal amount of reassurance should always be a part of medical therapy. These patients need both physical and mental rest and we frequently employ phenobarbital in doses of 16 to 32 milligrams three times a day along with "superficial" psychotherapy in an attempt to afford the patient this necessary relaxation.

From the purely medical aspect of ulcer therapy there are three things of importance in the control of acidity and the ulcer. These are the diet, and the employment of antacids and antispasmodics.

Diet

Lenhartz (15) first utilized the multiple-feeding technique in the treatment of the ulcer patient. This rapidly replaced Leube's starvation regimen. The excellent results of Lenhartz' multiple-feeding schedule was confirmed by subsequent investigators. Meulengracht (16), although often given credit for originating this method, merely re-awakened interest in Lenhartz' original work. Other more specialized dietary methods have been introduced from time to time. The most widely recognized regimens are those of Bertram Sippy (17) and Asher Winkelstein (18). The Sippy regimen, consisting of milk and cream with Sippy powders (magnesium oxide, calcium carbonate, and sodium bicarbonate), has been modified greatly and is adhered to less and less. There are many reasons for the modification of Sippy's regimen. It was nutritionally inadequate during the first three weeks, being especially low in vitamin C, and it did not result in as effective a control of gastric acidity as originally thought. The strictness of the diet was disliked by many patients and it did not seem to influence greatly the incidence of ulcer recurrence. Asher Winkelstein was concerned about the number of ulcer patients suffering from nocturnal pain. Since ulcer patients generally have a high rate of nocturnal acid secretion, Winkelstein modified his original intragastric drip method. Under his new regimen he allowed the patients to have three liberal bland meals per day and added sedatives, antacids, and atropine at various intervals during the daytime. In addition he ran a constant milk drip through a gastric tube between each meal and throughout the night. Although this strenuous therapy may be necessary in exceptional cases, it has been our experience that the relief of acute episodes can be just as effectively maintained by less strenuous measures. The problem of immediate relief has not been of great concern. The greatest problem has presented itself in the question of long-term treatment and the prevention of recurrences. Winkelstein's regimen has not solved this matter and it is our belief that these patients do better over a long period of time when there is as little interference as possible with the normal diet. To this end we have routinely employed a modified Meulengracht diet (Table 1).

This diet avoids the unpleasantness of intubation, as is required in the Winkelstein regimen. It affords the patient adequate calories and vitamins, and has been shown to be just as effective in controlling acidity, relieving pain, and healing the ulcer (19).

TABLE 1

Beverage
Milk, milk beverage, coffee substitute.

Bread
Bread (day-old) or toast (white or rye), soda crackers, zwieback.

Cereal
Cornmeal, farina, hominy grits, oatmeal, prepared corn cereal, prepared rice cereal rice, fine whole wheat cereal, other wheat cereal, strained.

Dessert
Bread pudding, cake (plain), cookies (plain), cornstarch pudding, custard, fruit puree whip, gelatin dessert, ice cream or ice (plain or with fruit puree), junket, rice pudding, tapioca pudding.

Fat
Butter or vegetable shortening.

Fruit
Any fruit puree or juice, fresh banana, canned Royal Anne and Bing cherries. Peeled and cooked: apples, apricots, peaches, pears, plums, prunes, rhubarb.

Meat or substitute
Beef, lamb, pork, veal: roast, boiled, broiled, baked.
Cheese: American (finely divided and in combination with other foods), cottage, cream.
Chicken: stewed, creamed, broiled, baked.
Eggs: coddled, poached, soft cooked, hard boiled, creamed, scrambled in a double boiler.
Fish: fresh, canned salmon or tuna: boiled, broiled, baked, creamed.
Liver: boiled, baked, creamed.
Oysters or sweetbreads: stewed, creamed, escalloped.

Potato or alternate
Prepared in any way except fried: macaroni, noodles, rice, spaghetti, Irish or sweet potatoes.

Seasoning
Salt.

Soup
Creamed soup made from allowed vegetables.

Sweets
Sugar, syrup, jelly, and chocolate.

Vegetables
Puree: string beans, beets, corn, peas, spinach, tomato.
Cooked tender: asparagus tips, carrots, egg plant, pumpkin, squash.

Avoid
1. Highly seasoned foods and sauces, catsup, horse radish, mustards, pickles and condiments.
2. Cabbage, onions, peppers, radishes, and turnips.
3. Rare meat, meat soup, broth and gravy.
4. Corned beef, frankfurters, sausage, smoked meat and fish, or any prepared nuts.
5. Fried food, hot bread and pastry.
6. Nuts.
7. Very hot and very cold food, unless eaten slowly.
8. Overeating.

Sample Menu

Breakfast	*Noon*	*Evening*
Orange juice	Creamed chicken	Strained cream of tomato soup
Cream of wheat	Mashed potatoes	Scrambled eggs
Toast	Green bean puree	Baked potato
Butter	Bread	Pea puree
Beverage	Butter	Bread
Cream	Lemon cream pudding with meringue	Butter
Sugar, if desired	Milk	Applesauce
		Milk

Midmorning, midafternoon and evening: Milk or milk beverage, crackers, cookies, bread or cereal.

Antacid therapy

As far as antacid therapy is concerned, we have found magnesium trisilicate and calcium carbonate to be as effective, or in many instances, more effective than amphojel®, phosphojel®, sodium bicarbonate or any of the many mixtures placed on the market under various commercial names. Magnesium trisilicate was first introduced by Mutch (20) in 1936. It has a gradual and prolonged action and reacts with acid by a dual mechanism. It acts as an absorbent and, in addition, reacts chemically with acid thus:

$$Mg_2SiO_3 \cdot 2H_2O + 4HCl \rightarrow 2MgCl_2 + SiO + 4H_2O$$

The effectiveness with which it reacts has been demonstrated repeatedly both *in vitro* and *in vivo*. Magnesium trisilicate is nontoxic and without serious side effects. We have never seen diarrhea of any serious degree develop. Since the magnesium ion, however, may tend to cause diarrhea in some patients it may be feasible to alternate this drug with calcium carbonate, an equally effective antacid. It is our practice to use either one, in dosages of 1 to 2 grams six times daily.

Antispasmodics

The use of antispasmodics has been incorporated into the routine therapy of peptic ulcer. We usually employ tincture of belladonna in a dosage of 15 to 30 drops four times daily. It has been our experience that this preparation is just as effective as many of the newer synthetic antispasmodics. If methantheline (Banthine®) bromide is chosen, a word of warning regarding its use in the presence of partial obstruction should be issued. We have seen occasional cases seemingly become more and more obstructed during the use of Banthine. The primary action of this drug is to cause a decrease in gastric motility and tone. In the face of partial obstruction this loss of tone may result in serious gastric distention and retention. These observations have been repeatedly made in the literature. The initial encouraging reports regarding the use of Banthine are being overshadowed by less enthusiastic or even adverse results. Of great interest is the recent report of Liebowitz *et al.* (21) in which they demonstrated the rapid development of refractoriness to the use of Banthine. During their investiga-

tions a dose of as much as 1.8 grams was given daily without maintaining depressant effects on gastric motility and secretory rate.

The blocking agents, hexamethonium salts and tetraethyl ammonium chloride and bromide, have been too variable in their effects on acid and too constant in side effects, to warrant their inclusion in the treatment of peptic ulcer. Postganglionic depressing agents such as dibutoline have been found to be less effective than either atropine or Banthine.

Miscellaneous

There have been many substances advanced as ulcer cures or as substitutes for the standard ulcer therapy of which we have written. Of these, gastric mucin has already been mentioned. There has been no evidence to show that it materially benefits the ulcer patient. Enterogastrone, a substance liberated by the intestinal mucosa in response to the ingestion of fats and inhibiting motor and secretory activity of the stomach, has been claimed to be effective both in animals and in man in preventing and healing peptic ulcers. More recent studies by Grossman (22), Pollard (23), Wollum (24), and other investigators have shown this hormone to be ineffective. There has appeared no proof regarding the effectiveness of other similar extracts, *e.g.*, preparations of hog stomachs and duodenum (mucosal and submucosal), desiccated and defatted raw whole mammalian duodenum (Viodenum®) or unspecified protein-free preparations of stomach or small intestine (Robuden®). Detergents have not been shown to be effective in man. The use of the newer cation exchange resins (Resinat®) have not been of material benefit thus far in the treatment of peptic ulcer. Martin and Wilkinson (25) have emphasized the importance of mesh or particle size in the use of resins, and further investigation along these lines may yet produce a more effective drug in the therapy of peptic ulcer. Combinations of various drugs (Carmethose, Mucotin, Resmicon, Chloresium powder) have given unspectacular results. X-ray therapy has been used in the treatment of peptic ulcer. Ricketts, Palmer, Kirsner, and Hamann (26) have shown that the percentage of patients whose ulcers heal, when x-ray therapy is given to the corpus and fundus of the stomach, is increased from 70 per cent when medical therapy alone is used, to 94 per cent when appropriate x-radiation therapy is added to the medical regimen.

SUMMARY

In the past twenty years many new methods have been proposed in the treatment of peptic ulcer. Critical evaluation of the results of these "advances" leads to the conclusion that peptic ulcer is still best treated by the simplest and time-tested procedures. These include the physician's genuine interest in the patient's problems, the enforcement of physical and mental rest with so-called "superficial psychotherapy," liberal amounts of reassurance, sedation as necessary, the use of a liberal bland diet, tincture of belladonna, and an antacid such as calcium carbonate or magnesium trisilicate. Although many false starts have been made along new lines of therapy during the past few decades, there is hope that some specific form of treatment may result from continued investigation in this field.

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CANCER OF THE STOMACH IN OLD AGE

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It is well known that cancer of the stomach is a leading cause of death among all types of malignant disease. Fewer than 10 patients of every 100 seen with cancer of the stomach will live for five years. The reason for this dismal outlook is generally regarded as based upon two facts in the natural history of the disease: 1) the insidious onset, preventing early diagnosis, and 2) the invasive nature of most of the tumors, involving by extension or metastasis neighboring and irremovable structures, even if the lesion itself is not large or of long duration.

What is the effect of age upon the outlook? In Figure 1 is given the age distribution, hospital mortality rate, and additional deaths within one month of operation in a personal series of 100 consecutive patients who underwent surgery.[1] The median age in this series was 60 years. As might be expected, there was a higher mortality in older patients, both in the hospital and after discharge in the first postoperative months. There was thus a 10 per cent hospital mortality rate in patients 60 years of age or older, and an additional 15 per cent in the first month, contrasting with a 2 per cent hospital mortality rate and a 2 per cent additional mortality in the first month in the younger group. (All of these additional deaths within one month were in patients whose disease precluded a resection.) Figure 2, however, brought to light an unexpected finding, in that the rate of "resection for cure" in older patients was substantially less than that in younger patients. It is frequently believed and taught that malignant disease is "more benign" in elderly patients than in the young, and remains in a form with which surgery may cope for a longer period of time. This belief is not borne out by the present study. A resection for cure was possible in only 40 per cent of the patients older than 60 years, whereas it was possible in 60 per cent of the younger patients. "Resection for cure," as used in this paper, means that at the time of operation all gross tumor had been removed; it does not include any type of palliative procedure. A usual rate for five-year survival is 25 per cent of those who have undergone a resection for cure; the remainder will succumb to recurrence. In this series, then, it is unlikely that there will be more than 5 five-year survivors among the 51 patients in the older age group.

The decreasing likelihood of cure with advancing age is demonstrated in patients over 70 years of age. There were 16 such patients in the present series, and it was possible to attempt a resection for cure in only 5; 1 of these died of the operation. Two of the remainder are already dead of recurrence fifteen and

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[1] In the period studied, the surgical staff saw in consultation about 85 per cent of all patients upon whom a diagnosis of cancer of the stomach had been made; operation, at least for the purpose of tissue diagnosis, was advised in all but 2 of the patients the writer saw in consultation.

twenty-one months, respectively, after resection. The other 2 are 79 and 80 years old, and their normal life expectancy is less than five years!

It may be argued that the lower rate of resection in the older patients is because the surgeon is unwilling to attempt procedures of great magnitude in the elderly. This is undoubtedly a factor in an occasional patient in whom it seems unwise to attempt a block excision of multiple organs in an elderly patient enfeebled by other diseases, in contrast to what might be attempted in a younger patient whose health is otherwise sound. But it is not a decisive reason for the lower resection rate, as shown in Figure 3. Here it is seen that there is roughly

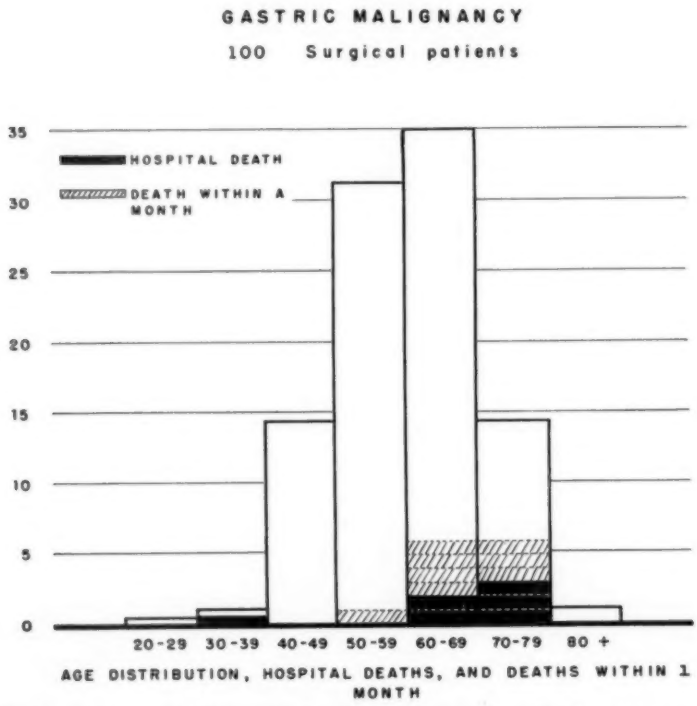

FIG. 1. The hospital mortality rate for the entire series of 100 patients was 6 per cent but it was 2 per cent in patients under 60 years of age, and 10 per cent in patients 60 years or older. The additional deaths within one month were all in patients who had no surgery, beyond a biopsy or a palliative procedure.

the same rate of "complicated resection" in the older patients as in the younger group. By "complicated resection" is meant a total gastrectomy, a subtotal gastroesophagectomy, or a subtotal gastrectomy including part of the liver, pancreas, or colon. This chart demonstrates also that elderly patients can survive these complicated resections with a mortality rate which need not be a forbidding one. The present writer some years ago performed a total gastrectomy on an 87-year-old man. The patient was naturally thin (weighing less than 100 pounds) alert and active, had a sound heart, lungs, and kidneys, and hence was essentially a good operative risk. He survived the operation without event, only to die of inanition some three months later; autopsy showed no evidence of cancer. The following case report of a patient included in the present series demonstrates

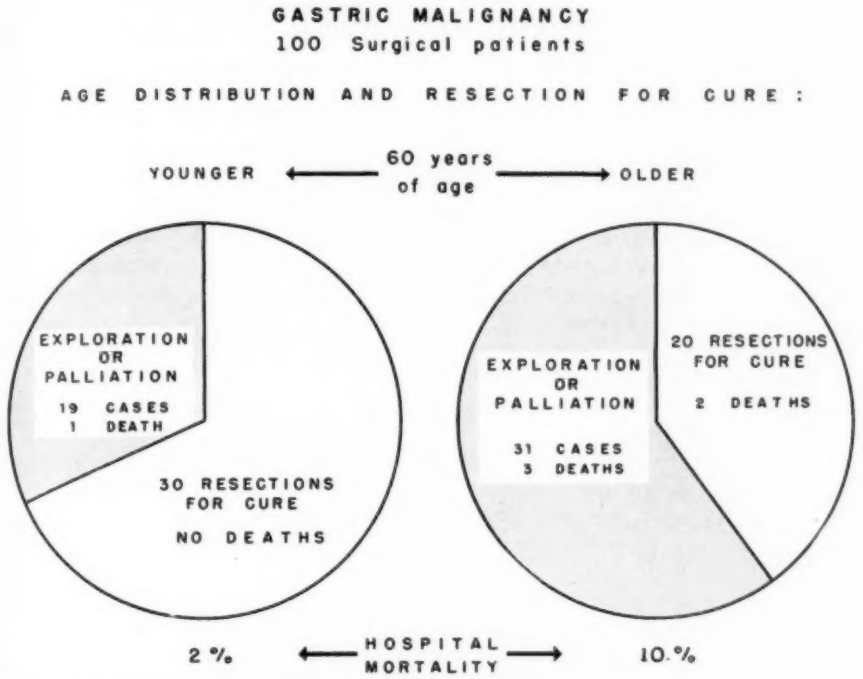

FIG. 2. There were only 2 deaths among 50 resections for cure, or 4 per cent; both were in the older age group. One patient was 79 years old and had a splenectomy and removal of the omentum as a first stage toward a proposed later resection; the gastric carcinoma perforated after this procedure, resulting in death. The second patient was 64 years old and died after a total gastrectomy, from an anastomotic leak.

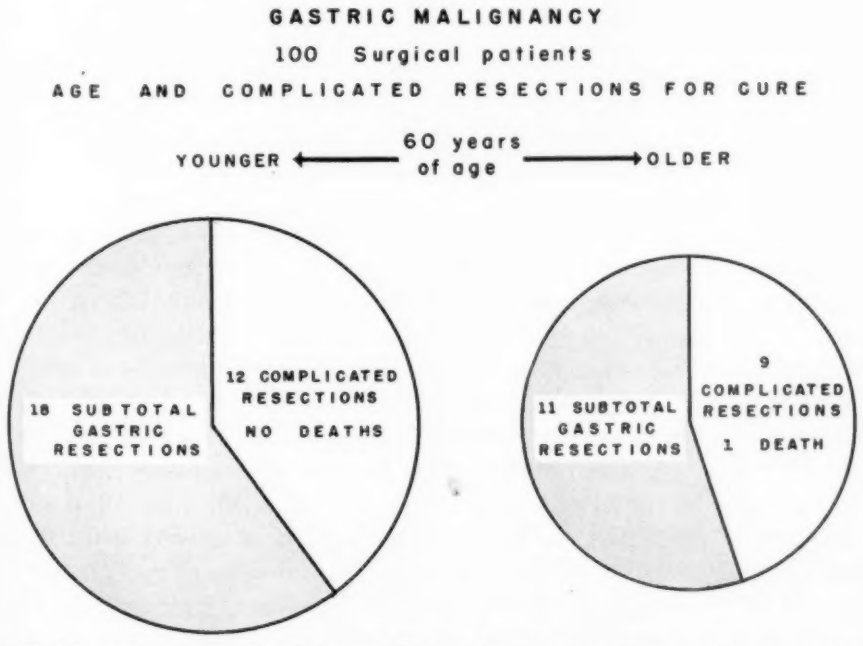

FIG. 3. The ratio of complicated resections to simple subtotal gastrectomy was the same for patients of all ages in this series. The complexity of the resection seemed to have little bearing on mortality rate.

that even poor-risk elderly patients may be brought through a formidable operative procedure if circumstances seem to warrant:

Case 1. The patient, a 77-year-old Catholic nun, was admitted to the hospital for evaluation of a hard, irregular, slightly movable epigastric mass at least 8 cm. across. She had suffered from mild anorexia following a hemorrhoidectomy performed in another hospital six months before, and she had lost 6 pounds in weight in the preceding three months. She had been a known diabetic and had had mild hypertension for at least seven years; the diabetes had usually been controlled by diet alone. The patient was moderately obese; her height was 63 inches and her weight about 140 pounds. The past history revealed that there had been a cholecystectomy and a mastectomy for carcinoma of the breast eight years and seven years before, respectively. The results of gastric x-ray examination were consistent with carcinoma of the stomach.

At operation on June 21, 1950, a bulky tumor of the greater curvature of the stomach was found, extending into the transverse mesocolon and compromising the blood supply of the colon. There was no evidence of distant metastases, although the right lobe of the liver could not be palpated because of the adhesions from the cholecystectomy. A subtotal gastrectomy with simultaneous transverse colectomy was carried out. An end-to-end anastomosis in the colon was performed and a catheter was led out, proximal to this anastomosis. A feeding jejunostomy was constructed.

Postoperatively the patient required two pints of blood for an unexplained anemia, and a wound infection developed. She was convalescing satisfactorily at the time of discharge on the eighteenth day after operation.

The patient did well symptomatically for about fifteen months, although a mass which was probably a recurrence could be palpated in the right lobe of the liver seven months after operation. She failed gradually over a six-month period and expired twenty-one months after the operation at the age of 79 years.

Comment: A moderately obese, mildly diabetic, 77-year-old patient withstood simultaneous subtotal gastrectomy and transverse colectomy and lived for twenty-one months; there was good palliation for about fifteen months.

It may be concluded, therefore, that approximately the same criteria of operability are employed in the operating room for patients of all ages. Why, then, is there such a relatively poor showing in older patients? A study of the histories of the 16 patients 70 years of age or older showed that the duration of symptoms had been six months or less in 9 patients, from six months to a year in 3 patients, and longer than a year in 4 patients. Thus the time lag from first symptom to operation is not strikingly different in the elderly patient from that in the younger one. Interestingly enough, in 2 of the 4 patients whose symptoms had continued for longer than a year, it was possible to perform a resection for cure. There was one feature of interest in the histories given by these patients over the age of 70: in half there had been a striking loss of weight (25 to 50 pounds) and in only 1 had there been no weight loss. This might constitute a hint for the family physician charged with the overall care of the elderly patient. Any unexplained loss of weight in an elderly patient, even if only 3 or 4 pounds, should raise the possibility in the physician's mind of the existence of gastric malignancy. The importance of suspecting gastrointestinal malignancy in association with any change of dietary or bowel habit in elderly patients has been shown repeatedly by students of the subject.

Given the diagnosis of cancer of the stomach, are there elderly patients who

should not be operated upon? It is the contention of the writer that nearly every patient with this disease deserves to have a tissue diagnosis made, even if a resection for cure may not be attempted. The rationale for this belief rests on two facts, the first of which is that more than 5 per cent of gastric malignancies are radiosensitive tumors. (In the present series there were 2 cases of Hodgkin's lymphoma, 2 cases of reticulum-cell sarcoma, and 3 cases of lymphosarcoma—roughly, 7 per cent.) Some of these patients will have long periods of palliation as a result of x-ray treatment, with or without operation. The second fact is that clinical determination of inoperability is very unreliable. In the writer's experience, "hepatic metastases" detected by abdominal examination have proved to be cirrhosis of the liver, a rectal shelf has been shown to be an

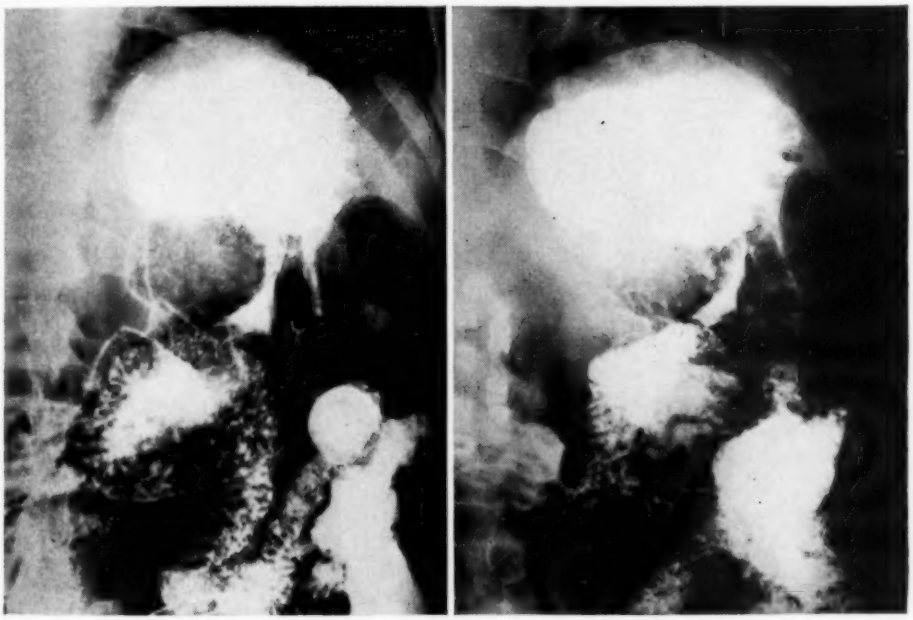

FIG. 4. X-ray films of the stomach of a 79-year-old patient (Case 2), showing a large ulcerated neoplasm in the upper half of the stomach.

incarcerated retroverted uterus, and ascites has proved to be obesity. Inoperable extension as determined by roentgenogram, or by the palpation of an apparently fixed mass, has likewise proved to be erroneous in the experience of every surgeon who has been able to persuade the internist to permit operation despite these clinical deterrents. Even the nature of the growth may be misinterpreted, as shown in the following case report:

Case 2. The patient, a 79-year-old man, was admitted for treatment of what was presumably a gastric neoplasm. He had been found to be markedly anemic nine months previously, and had been given four pints of blood in a hospital. Three weeks before admission he had experienced a massive hematemesis, requiring six pints of blood for treatment. Gastric x-ray examination (Fig. 4) showed what was interpreted as a large ulcerating neoplasm of the stomach; the possibility of a smooth-muscle tumor was considered.

The patient's general condition proved to be excellent, and he was operated upon December 23, 1952. There was a bulky tumor of the posterior gastric wall (Fig. 5), well localized, and grossly benign. Frozen section showed that it was a well differentiated leiomyosarcoma. There was no evidence of metastases. It was possible to perform a local resection of the tumor with adequate gastric margin through an anterior gastrotomy. The procedure consumed very little time, and the patient's postoperative course was entirely uneventful. He was discharged on the sixth day after operation.

Comment: It was deemed probable beforehand that either the lesion would be found inoperable, or that a rather high gastric resection would be necessary. Instead, a very

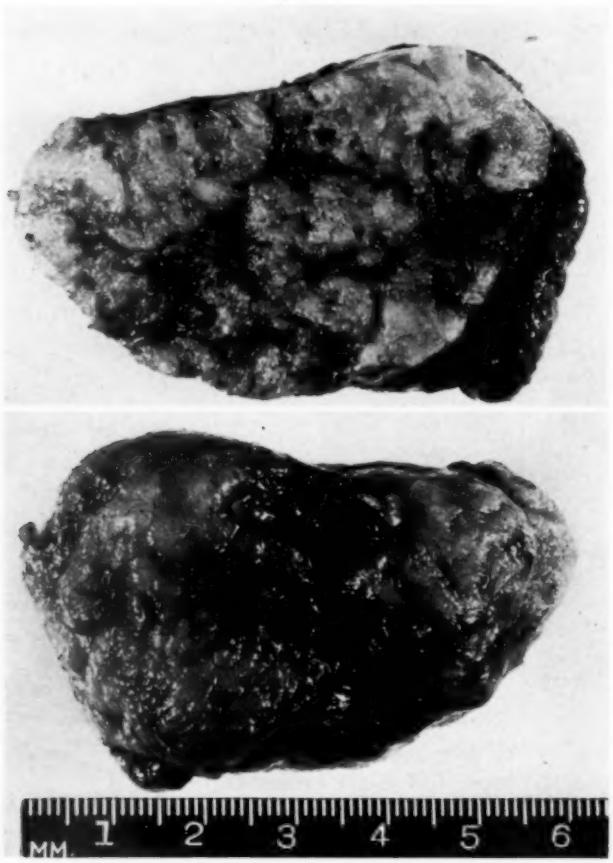

FIG. 5. Photograph of the specimen removed in Case 2. This tissue proved to be a slowly growing leiomyosarcoma which could be excised locally without a major resection.

simple procedure was easily executed, and gave reasonable promise of relieving the patient's symptoms of anemia and hemorrhage for the duration of his life.

There will, of course, remain a very small proportion of patients in whom an operation—even for tissue diagnosis—may be deemed inexpedient. There will be the rare patient in whom the internist can state with certainty that, because of some other severe disorder, life expectancy is so short that death will occur before the advancing cancer of the stomach can reach its fatal outcome. There will also be an occasional very old patient whose symptoms are minimal, and

in whom the hazard of even a simple exploration is unduly great, either by reason of severe associated diseases or, more rarely still, by reason of the location of the tumor, *e.g.*, at the cardia. The following case report is representative of a rare instance in which absence of symptomatology justified postponement of surgical intervention:

Case 3. The patient, a man now aged somewhere between 84 and 88 years, was first seen in 1941 because of acute urinary retention. He gave his age then as 76 years. A transurethral resection was performed after preliminary decompression, but the blood urea level remained elevated to 93 mg. per cent, and renal function was repeatedly demonstrated to be poor. In 1942 there was another admission because of azotemia due to a urinary tract infection; the blood urea dropped from a level of 171 mg. per cent to 90 mg. per cent. In 1943 a diagnosis of pernicious anemia was made (treated since then with liver) and he underwent gastric x-ray examination, because of mild dyspepsia. The films showed several filling defects in the gastric antrum, interpreted as gastric polyps, probably benign. These filling defects were demonstrated again in 1944.

The patient was occasionally seen in intervening years, usually with urinary tract difficulties, and in 1950 new gastric x-ray films were obtained because of mild epigastric discomfort. These films were interpreted as follows: "Polyp of antrum demonstrated. Filling defect and destruction of mucosal pattern lesser curvature of antrum, probably representing carcinoma." In view of the patient's advanced age, the minimal symptoms, and the very poor renal function, no surgery was advised. In a follow-up through his physician in December, 1952 (at which time he gave the age of 84 years), two and one-half years after a diagnosis of probable gastric carcinoma had been made, it was revealed that the patient was pursuing his usual habits and had no gastrointestinal symptoms. He refused to have further gastric x-ray examination.

Comment: In a younger patient, with better kidneys, a gastric exploration would certainly have been in order in 1950, if not sooner, because of pernicious anemia (in which the incidence of gastric cancer is known to be high) and gastric polyps, to say nothing of a probable cancer. The patient's benign course has justified the contrary advice given this particular patient.

SUMMARY AND CONCLUSIONS

A study of the patients in this series appears to show that the chance of effecting a surgical cure for cancer of the stomach diminishes with advancing years. The reason for this is not altogether clear, but one may speculate that elderly patients have blunted sensibilities, rendering them impervious to early warning symptoms which younger patients heed. Moreover, the elderly (and their physicians) are likely to accept progressive physical impairment as a natural result of the aging process, rather than to suspect some new cause, like cancer of the stomach. The study suggests that unexplained weight loss of even a few pounds should cause one to suspect gastric malignancy in the aged, as should also any change in eating habits, however slight. Once the diagnosis of gastric malignancy has been made, nearly every patient should be given the privilege of a surgical exploration to determine operability and to obtain tissue for pathologic diagnosis. Clinical evidence of inoperability may be very misleading; and more than 5 per cent of patients will prove to have a radiosensitive tumor. Although there is the expected increase in operative mortality for patients over 60 years of age, this does not exceed about 10 per cent even for complicated resections, and is justified by the possible benefit to the patient. Elderly patients

will tolerate extensive resections, and often experience satisfactory palliation, if not cure.

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LABORATORY PROCEDURES IN THE DIAGNOSIS OF DISEASES OF THE PANCREAS[1]

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The purpose of this paper is to discuss some of the laboratory procedures which may be helpful in the diagnosis of certain diseases of the pancreas. They include the determination of the degree of enzyme activity in blood serum, duodenal juice, urine, feces and peritoneal fluid, the microscopic examination and chemical analysis of stools for evidence of impaired fat and protein digestion, the glucose tolerance test and the examination of duodenal juice for exfoliated malignant cells. In addition, reference is made to other laboratory tests which may reveal abnormalities in pancreatic disease, such as the serum calcium concentration, the differential white blood cell count and the various liver tests. The procedures are discussed from the standpoint of their clinical usefulness rather than from that of the technique of their performance.

A. PANCREATIC ENZYMES IN SERUM

Procedures are available for determining the amylase and lipase activity of serum. The plasma antithrombin titer, believed to reflect tryptic activity, is currently being evaluated in pancreatic as well as in other diseases.

1. *Serum amylase*

Four methods have been used for estimating the amylolytic activity of serum. These are the viscometric (1), the starch-iodine (2), the nephelometric (3) and the saccharogenic (4, 5). The viscometric method depends upon changes in viscosity of a starch-enzyme mixture as the starch is hydrolyzed by the enzyme. The range in normal subjects extends from 4.2 to 7.2 units (6, 7). False values sometimes occur as a result of a decrease in viscosity independent of enzyme action, when the starch and serum are first mixed (8). The iodine method depends on the disappearance of an iodine-starch blue color as the hydrolysis of starch occurs. It may yield unsatisfactory results in the presence of hyperbilirubinemia or when the serum is discolored (8). The normal range of values is from 0.0011 to 0.0071 Norby units (3, 9). The nephelometric method, which employs the Tyndall phenomenon for measurement of the concentration of substances in suspension, measures the amount of glycogen remaining when glycogen, instead of starch, is used as a substrate. The saccharogenic (copper reduction) method of Somogyi is the most generally used and the most accurate; it requires about one hour for its performance. The usual range of values for

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normal subjects extends from 60 to 180 units (mg. of glucose per 100 ml. of serum). The method involves the determination of the amount of glucose formed when starch is hydrolyzed by the amylase. A marked hyperglycemia may interfere with its accuracy (8).

The serum amylase test is most useful in the diagnosis of acute pancreatitis (10). In this disease the serum amylase is increased more than from 4 to 6 times the normal level early in the attack and usually returns to normal within three to four days in uncomplicated cases. Persistent elevations (up to twenty-two days) indicate a continuation, extension or progression of the process (11). The height of the amylase level bears no constant relationship to the severity of the attack. The concentration may also be increased during the acute episodes of chronic relapsing pancreatitis, particularly early in the course of the disease. Subsequently, as the pancreas becomes progressively and extensively damaged, the functioning acinar cells may be too few to produce an elevation during the painful seizures.

The serum amylase concentration may be increased in patients with carcinoma of the head of the pancreas (12), but not as a rule when only the body or tail is involved. It may also be increased when a peptic ulcer penetrates in or near the pancreas and when free perforation of an anterior duodenal ulcer occurs into the peritoneal cavity (13, 14). In the latter instance, the hyperamylasemia is attributed to absorption of the enzyme from the peritoneal cavity. Elevated values may also be found when renal function is impaired (paralleling the degree of azotemia), in peritonitis due to various causes (15), in intestinal obstruction (13, 14), and in mumps (16) with or without orchitis. An elevation in mumps, in the absence of pancreatitis, is not accompanied by an elevation in the serum lipase level. Increased values, as well as normal and low values, have been reported in hepatic disease (17). The elevations in serum amylase concentration which occur in conditions other than acute pancreatitis are usually not as high (less than 4 to 6 times normal) as those encountered early in acute primary pancreatic inflammation. Amylase is detectable in the serum after total pancreatectomy in the human, the source of the amylase presumably being extra-pancreatic tissues, such as the salivary glands, liver and intestine.

Recently cause for confusion in the interpretation of values for serum amylase has arisen as a result of the reported elevations in the sera of patients given opiates (18–20). The problem raised by this possibility is an important one, because reliance cannot be placed on the test when a patient with abdominal pain presents himself for diagnosis after he has received an opiate. Some of the data upon which the contentions are made, however, are as yet inconclusive and more are required. For example, the actual increases in the serum amylase level following a subcutaneous injection of 16 mg. of morphine sulphate in the 3 instances reported by Burke *et al.* (18) are less impressive than the percentile increases, in view of the fact that they all occurred within the normal range of values (39 to 60, 20 to 56, and 24 to 80 units)—the normal range in their laboratory being 6 to 99 units. Moreover, doses of codeine sulphate (2 grains) larger than those ordinarily administered, have been reported to give rise to

significant elevations in the serum amylase and lipase levels in 6 of 27 cases (20). An increased amylase level has been reported following an unstated amount of Demerol in 1 patient (21).

2. *Serum lipase*

The lipase activity of serum is determined by titrating, with a standard solution of sodium hydroxide, the fatty acid liberated as a result of hydrolysis of a neutral fat substrate (olive oil emulsion) by the lipase. The test, when olive oil is used as a substrate as in the Cherry and Crandall (22) method, requires about twenty-four hours for its performance. Since decisions concerning management must often be made promptly in patients with acute abdominal pain, the 24-hour period required for the completion of the test mitigates against its usefulness in the diagnosis of acute pancreatitis. Values above 1.0 ml. N/20 NaOH are considered to be of significance by some (15, 17, 23, 24), and above 1.5 cc. N/20 NaOH by others (25, 26).

The serum lipase activity is increased early in an attack of acute pancreatitis and may remain elevated after the serum amylase activity has returned to normal (23, 26). It may also be increased early in the course of carcinoma of the head of the pancreas, when the lesion obstructs the pancreatic ducts; it decreases as the acinar cells become progressively destroyed (24). Thus, the serum lipase test is of value in the diagnosis of pancreatic carcinoma, only when elevated values are obtained. Elevated serum lipase values have been reported in some patients with cholelithiasis and jaundice (24), hepatic tumor (24), viral hepatitis (17), hepatic cirrhosis (17, 24), intestinal obstruction (15, 24, 27) (also in experimental ileus (28)), peritonitis (15) and following large doses of codeine sulphate (20). Lipase is detectable in the serum after total pancreatectomy in the human, the source presumably being the stomach and the intestine.

3. *Plasma anti-thrombin titer*

Thus far, a satisfactory direct method for estimating serum trypsin has not been available. However, Innerfield *et al.* (29) have postulated that the plasma antithrombin titer reflects the blood trypsin content. They have found the antithrombin titer to be elevated in acute pancreatitis, in some cases of chronic relapsing pancreatitis, pancreatic cyst, and carcinoma of the pancreas associated with jaundice of less than six weeks' duration; but not in other types of acute abdominal conditions or in obstructive jaundice of nonpancreatic origin, incarcinoma of body or tail of the pancreas, in most instances of fibrocystic disease of the pancreas, or in liver disease (29). In serious liver disease, decreased titers have been observed (30).

B. PANCREATIC ENZYMES IN URINE

The determination of the concentration of amylase in the urine was widely used for many years for the diagnosis of acute pancreatitis. More recently it has been employed less often, because examination of the blood serum for amylase has been found to be of greater diagnostic value. The determination

of urinary lipase (31) has not been widely used, and a satisfactory method for determining urinary trypsin is not available.

1. *Urinary amylase*

The methods for determining amylase activity in serum are applicable to urine, but larger quantities of urine than of serum are necessary, because urine has less amylolytic activity than serum. The saccharogenic method, modified (32, 33) to correct for the normal reducing qualities of urine, is the most satisfactory. It is less satisfactory when a marked glycosuria is present, and random specimens may be misleading because of a lack of relationship between the blood and urinary amylase (8, 32, 33, 34). The normal range of urinary amylase according to Nothman (35), using the Somogyi saccharogenic method (4), varies from 80 to 350 units per 100 ml. and according to Dozzi (8, 32), also using a saccharogenic method, from 264 to 953 mg. per 100 ml. of urine per twenty-four hours. The urinary amylase determination may be useful occasionally when acute pancreatitis or an acute episode of chronic relapsing pancreatitis is suspected, as the urinary amylase level may remain elevated after the serum amylase level has already returned to normal.

C. PANCREATIC ENZYMES IN DUODENAL JUICE

The determination of the bicarbonate and enzyme content of duodenal juice, aspirated before and after the intravenous or subcutaneous injection of a suitable stimulant of the external secretion of the pancreas, can supply helpful information concerning pancreatic disease (36, 37). The procedure is time-consuming and requires an elaborate set-up. Gastric juice and duodenal juice are aspirated and collected separately by continuous suction, using either two single-lumen tubes tied together (38) or a double-lumen gastroduodenal tube such as that of Ågren and Lagerlof (39), or of Abbott and Rawson (40). By the use of such an arrangement, most of the gastric juice and the greater part of the duodenal content (bile and pancreatic juice) are withdrawn separately through the two lumens.

The procedure necessitates the proper placement of the tube tips. This is best accomplished under fluoroscopic guidance. The gastric tube is intended to prevent gastric juice and swallowed saliva from entering the duodenum. The duodenal tube tip should be at or near the ampulla of Vater. Basal secretion is collected for a period of twenty minutes, after which a suitable stimulant is injected, and 3 to 4 successive twenty-minute samples of duodenal content aspirated. The substances used for stimulating pancreatic secretion include: secretin (1 clinical unit per kilogram of body weight, intravenously) (41, 42), mecholyl (15 mg. subcutaneously) (41) or urecholine (10 mg. subcutaneously) (43). Secretin evokes a large volume of juice rich in bicarbonate but poor in enzymes (hormonal secretion), whereas either mecholyl or urecholine produces a scant flow of juice poor in bicarbonate but rich in enzymes (neural secretion). Modifications of the Somogyi method for serum amylase, of the Cherry-Crandall method for lipase, and of the Riggs and Stadie (44) procedure for peptic activity are applicable for duodenal enzyme determinations. Bicarbonate content may

be determined by titrating 5 ml. of each specimen of duodenal juice with 0.1 N NaOH after acidification with 10 ml. of 0.1 N HCl.

Evidence of deficient pancreatic secretion may be found in patients in whom the pancreatic ducts are obstructed (as by carcinoma or calculus), or in whom a sufficient number of acinar cells are destroyed by inflammation, carcinoma or atrophy. Such evidence has been found in patients with carcinoma of the head of the pancreas, chronic pancreatitis, subsiding acute pancreatitis and extensive carcinoma of the body of the pancreas, but not in sprue or in obstructive jaundice when the duct of Wirsung is not obstructed.

D. PANCREATIC ENZYMES IN PERITONEAL FLUID

The determination of the concentration of amylase in peritoneal fluid obtained by abdominal paracentesis has been utilized by Keith *et al.* (45) in the diagnosis of acute pancreatitis. The concentration is increased and may remain so after the blood level has returned to normal. In addition, the appearance of the aspirated fluid may furnish some information as to the type of pancreatitis present; a yellow turbid fluid indicates the edematous type and a reddish brown color indicates the hemorrhagic form.

E. PANCREATIC ENZMYES IN FECES

Examination of the feces for enzymes is not a widely used method for the study of the external secretion of the pancreas. Amylase and trypsin are normally present in stools but lipase, which is inactivated by feces, usually cannot be detected. The amylase content of the stool varies from day to day depending upon the intake of food (46). Even with 24-hour samples, there is no constant relationship between the amounts of amylase in the stools of patients on the same diet or in the same person from day to day, although weekly totals approximate each other more closely. The admixture of enzymes from salivary glands, stomach and intestine further contribute to the unreliability of determining fecal enzymes as a test of the external secretion of the pancreas.

The gelatin-film test is used to gauge the trypsin content of the stools of infants with suspected fibrocystic disease of the pancreas. Fecal suspensions are placed on gelatin film (unexposed x-ray film) and incubated. If trypsin is present, the surface gelatin is dissolved (47). For each case, 3 specimens of stool are collected, unadulterated by urine. They should be examined within twenty-four hours. Feces are diluted 1:5 and 1:10 with distilled water. About 0.1 cc. of each suspension is placed on a strip of gelatin film clipped to cardboard. The film is kept at body temperature for one hour, or at room temperature for one and a half to two hours, then washed in a stream of cold water. Complete dissolution at the site of a drop indicates abundant enzyme activity. In an infant, if the results of the test are positive in 3 stool specimens, pancreatic fibrosis is unlikely. However, 3 negative results do not necessarily prove the presence of this condition. In doubtful cases duodenal fluid should be aspirated and its tryptic activity assayed. Great caution must be used in performing and interpreting the test, because proteolytic bacteria of the feces are capable of digesting

the gelatin on the film. A procedure for decreasing the concentration of bacteria by dilution is available (48).

F. MICROSCOPIC EXAMINATION AND CHEMICAL ANALYSIS OF FECES

Examination of the feces for undigested food may often supply evidence of an inadequacy of the external secretion of the pancreas (49, 50). In marked pancreatic insufficiency, the stool is bulky, glistening, pale in color due to the presence of fat, fatty acids and soaps, rancid in odor, and has the consistency of thick butter. The passage of feces consisting of masses of fat resembling butter or cream (steatorrhea), during ingestion of a diet containing considerable amounts of fat, is almost pathognomonic of pancreatic disease.

1. *Microscopic examination*

Microscopic examination of the stools in pancreatic achylia usually reveals large quantities of fat in the neutral form. Neutral fat appears as yellowish flakes or droplets; fatty acids, as flakes or needle-like crystals; and soaps, as amorphous flakes or rounded masses, as well as needle-like crystals. Sudan III when added to the stool stains neutral fat red, and free fatty acid, orange. Soaps (combined fatty acids) remain unstained unless the fatty acids are liberated by the addition of a drop of 30 per cent acetic acid and heating to the boiling point over a flame. Varying amounts of fatty acids may be found in the stools of patients with pancreatic insufficiency, as a result of their formation from neutral fat in the colon (35) by bacteria.

The finding, in the stool, of large numbers of undigested muscle fibers with preserved longitudinal and transverse striations (creatorrhea) during administration of a diet containing large amounts of chopped beef or ham given raw or lightly broiled, indicates a deficient digestion of protein. Muscle fibers, however, can be broken down by the intestinal bacteria in the presence of pancreatic insufficiency; hence, creatorrhea may be missed if the fecal material remains in the colon for a long time (35). The presence of starch granules (amylorrhea) in the stool is of little diagnostic importance. Starch granules stain blue on contact with Lugol's solution.

2. *Chemical analysis of feces for fat and nitrogen*

The determination of the fat and nitrogen content of feces during a fixed dietary intake of fat, protein and carbohydrate can supply important information in pancreatic disease. Usually the Schmidt diet (51), or a modification of it (35), is ingested over a period of three days. A readily identifiable substance, such as carmine or charcoal, is used to "mark off the stools." The usual procedure is to administer the carmine (0.3 Gm.) in a capsule with the first meal (35, 51). On the morning of the fourth day, charcoal (1 Gm.) is ingested with a breakfast consisting of milk. The stools are collected after beginning the test diet. The first stool containing carmine is saved, as are subsequent ones. The first stool containing charcoal is rejected. The stools should be preserved in alcohol (0.8 cc. of 95 per cent ethyl alcohol with each gram of stool) rather than kept in a freezer, because it has been shown that refrigeration does not prevent the splitting of neutral fat.

The Schmidt diet contains 105 Gm. of protein, 135 Gm. of fat and 180 Gm. of carbohydrate. In normal individuals, up to 6 per cent of the fat and up to 8 per cent of the nitrogen ingested while on such a diet are excreted in the feces (51). In complete obstruction of the pancreatic ducts, about 60 per cent of the ingested fat and about 50 per cent of the ingested nitrogen may be recovered from the feces. Most of this fat is in the form of neutral fat. In sprue the total amount of stool fat may also be greatly increased; however, the larger proportion of it consists of free and combined fatty acids, rather than of neutral fat. An increased amount of fat in the stools can also occur in common-duct obstruction and when intestinal transport is very rapid.

The fecal nitrogen content may be greatly increased (azotorrhea) in pancreatic insufficiency. It is usually within normal limits in common-duct obstruction and in sprue, although Comfort *et al.* (52) feel that it may also be increased in sprue. They believe that values for fecal fat and nitrogen are not important diagnostic aids in distinguishing between idiopathic and pancreatogenous steatorrhea, and that values for fecal nitrogen should not be used for differentiating between the two. Evidence of a diminished hydrolysis of protein in the intestines of patients with chronic pancreatitis has recently been obtained by the finding of an increased fecal excretion of orally administered I^{131}-labeled protein (53).

G. EXFOLIATIVE CYTOLOGY IN DIAGNOSIS OF PANCREATIC MALIGNANCY

Duodenal drainage may be of use in the diagnosis of carcinoma of the pancreas. The tube is placed so that the tip is near the ampulla of Vater and for this procedure, fluoroscopic guidance is practically essential. Separate collection of gastric juice and duodenal juice may be made, as described in the section on duodenal enzymes. The duodenal juice of patients with carcinoma, collected without stimulation, has been found to contain malignant cells by McNeer and Ewing (54) as well as by others. It would seem that the use of a stimulant (55) of the external secretion of the pancreas might increase the chance of finding cells. In the experience of Rubin *et al.* (56), the technique and modifications of staining as described by Lemon (55, 57) have provided satisfactory smears for diagnosis. The cytology of the duodenum is similar to that of the stomach, except that there are fewer squamous cells, and normal cells have a tendency to be arranged in plaques. Malignant cells have their usual appearance but their point of origin in the pancreas, liver, biliary tract or stomach cannot be determined (49). In the experience of Lemon and Byrne (58), tumors in the biliary tract and pancreas, less than 2 cm. in diameter, may exfoliate enough cells for detection by cytologic methods in advance of roentgen diagnosis.

H. GLUCOSE TOLERANCE

Investigation of the carbohydrate metabolism may have considerable diagnostic value in diseases of the pancreas. The oral glucose tolerance test may yield a diabetic curve in patients with steatorrhea of pancreatic origin, but a flat curve in patients in the active stage of sprue. Impairment of glucose utilization is detectable when sufficient islet-cell damage has occurred as a result of destruction by inflammation or carcinoma. Other evidences of deranged carbo-

hydrate metabolism may include hyperglycemia and glycosuria. Low values for blood glucose, as well as a tolerance curve indicative of increased utilization of glucose, may be obtained in islet-cell tumors.

I. SERUM CALCIUM

The serum calcium level may be lowered in acute hemorrhagic pancreatitis. The depressed values are usually observed within the third to fourteenth days after the onset of symptoms (23 and 59–64) and most frequently on the fourth and fifth days. The lowering of serum calcium level has been attributed (61) to the marked mobilization of calcium in and around the pancreas as a result of the formation of calcium soaps, with fatty acids liberated when neutral fat is hydrolyzed by the lipase released into the peritoneal cavity (63). Values as low as 5.1 mg. per 100 ml. have been recorded in the absence of tetany (65). In general the most seriously ill patients have the lowest serum calcium values, presumably because the amount of calcium withdrawn from the blood depends upon the extent of fat necrosis which, in turn, is influenced by the severity and duration of the disease.

J. LYMPHOCYTES

A significant reduction in lymphocytes in the differential blood smear in acute pancreatitis has been reported as occurring within forty-eight hours of onset (66). Differential values of 12 per cent or less were invariably noted at the first examination made within four hours to two days after onset. The greater the initial decrease in lymphocytes, the more likely was an extensive necrosis with an unfavorable course. Fairly rapid appearance of lymphocytosis after an initial lymphopenia indicated less severe inflammation and a better prognosis. The reduction in lymphocytes in acute pancreatitis probably represents a response to stress, and therefore may be a nonspecific phenomenon.

K. MISCELLANEOUS

Other laboratory findings, especially in acute pancreatitis, may include an elevated level of serum bilirubin, hypoprothrombinemia, positive results from, cephalin flocculation, colloidal red, thymol turbidity and thymol flocculation tests, hyperlipemia (67), ketonuria and bilirubinuria. In acute pancreatitis, hyperlipemia along with a milky serum has been observed to exist for weeks, and may be related to a deficiency of a fat-utilizing substance normally elaborated by the pancreas (67, 68). In destructive lesions of the pancreas, associated with steatorrhea, an impaired vitamin-A tolerance curve may be obtained.

SUMMARY

1. Various laboratory procedures which may be helpful in the diagnosis of pancreatic disease are presented and their application discussed. They include determination of the degree of enzyme activity in the blood serum, duodenal juice, urine, feces and peritoneal fluid, microscopic examination and chemical analysis of feces for evidence of fat and protein digestion, glucose tolerance test, examination of duodenal juice for exfoliated malignant cells, serum calcium concentration, liver tests and differential white blood cell count.

2. The serum amylase test is the most widely used procedure in making the diagnosis and in following the course of acute pancreatitis, as well as the acute episodes of chronic relapsing pancreatitis.

3. In the diagnosis of chronic pancreatitis, with or without calcification, the determination of the concentration of enzymes in aspirated duodenal juice before and after the administration of a suitable stimulant, the microscopic examination of stools for fat and meat fibers, the chemical analysis of feces for total and split fat and nitrogen and the oral glucose tolerance test are the most useful procedures.

4. The diagnosis of carcinoma of the pancreas is aided by the same procedures useful in the diagnosis of chronic pancreatitis. In addition, examination of duodenal juice may disclose exfoliated malignant cells.

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A CORRELATIVE ANALYSIS OF THE PATHOGENESIS OF HUMAN AND EXPERIMENTAL ARTERIOSCLEROSIS[1]

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INTRODUCTION

When experimental research has as its principal objective the specific analysis of human disease, it is often difficult to conduct the research continuously with the principal objective in mind. There is a tendency for the objective to undergo a subtle change, directed by positive results of the experiment. At times, this change is desirable and the knowledge which accumulates through diversion of interest is very valuable. At other times, the knowledge which accumulates is harmful because it directs the research effort away from the original objective. Therefore, it is useful to keep the problem in mind and to reflect at intervals upon the relations between the experimental trends and the human disease which is being studied by the experimental methods. This is the main purpose of the present article, which is concerned mostly with efforts in this laboratory to reproduce in the experimental animal forms of athero-arteriosclerosis which closely resemble the common forms of the human disease.

THE GENERAL PROBLEM OF HUMAN ARTERIOSCLEROSIS

Most of us believe that we know what arteriosclerosis is. There can be little conviction in this belief. Arteriosclerosis is not a simple process and not a disease entity. In general, it may be regarded as a complex mixture of degenerative and reparative processes which lead to increased rigidity, diminished elasticity and often decreased caliber of arteries. As a rule, these processes either develop or are accentuated at focal points, with a tendency to spread and become confluent. The processes have unpredictable vagaries of distribution. At times, they involve only local vascular segments; at other times, only certain branches of an organ system; and, at still other times, only branches of similar dimensions in several organ systems. Generalized arteriosclerosis, therefore, is a diagnosis which seldom describes the pathologic state. Little parallelism exists in the magnitude or basic character of involvement of different arterial systems and even branches of the same arterial system. In one patient, the processes may be severe only in the aorta. In another, the aorta may be lightly involved, whereas severe changes are apparent in the coronary arterial system. In still another patient, the cerebral arteries may be severely affected, with only minimal changes in the aorta or coronary arteries. The same observations apply not only to organ

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systems but also to branches, especially those of similar caliber in different organ arterial systems.

These facts direct attention to the conclusion that, if the exciting factor in the pathogenesis of human arteriosclerosis is a relatively inert chemical compound circulating in the blood plasma, the distribution of the structural effects of the exciting factor is non-uniform and therefore must be controlled by other factors, some of which must be local in nature and variable from place to place in the vascular system. Therefore, we can not neglect a search for local factors in the pathogenesis of arteriosclerosis, however desirable a single systemic explanation might be.

THE DEFINITION OF HUMAN INTIMAL ARTERIOSCLEROTIC SEQUENCES

Inasmuch as there is no single cause or definitive characteristic of arteriosclerosis, the process has been defined principally by microscopic structural changes. Unfortunately, there is no agreement as to the sequences in the structural changes or as to a common pathogenesis. Structural changes may occur in one part, or in all parts of the vascular wall. The most easily recognized changes are encountered in the intima. These seldom occur alone, and they can not be regarded as occurring prior to changes of less pronounced structural nature elsewhere in the vascular wall. The most important intimal change is essentially proliferative. This proliferative reaction, if undisturbed by degenerative changes, often results in the construction of a tissue which resembles that of the subjacent vascular wall. Thus, the reaction may be regarded as a reparative process. The orientation of the proliferating fibroblasts, the deposition of collagen between them, the new formation of elastic tissue, and even the differentiation of fibroblasts into smooth muscle cells, indicate that local conditions have stimulated the proliferating tissues to build a structure which resembles that of the subjacent vascular wall.

It would seem that this biologic reaction is a natural response to circulatory conditions. Seldom, however, does this response proceed to perfect vascular reconstruction. Usually, the reaction is modified so that fibrous elements predominate and undergo degenerative changes of a mucinous or hyalin character. Also, there is often, particularly in proliferating intima of large arteries, an accumulation of lipids, especially cholesterol and its compounds. Coincidentally, many macrophages appear and yellowish fatty plaques are formed. These areas deteriorate and excite inflammatory reactions, usually accompanied by ingrowth of capillaries from the adventitia or vascular lumen. Hemorrhage from the newly developed capillary network is common. This frequently causes acute swelling of the plaque with superficial necrosis and subsequent thrombosis, leading to occlusion of the lumen of the vessel. A less significant degenerative change in the hyalinized mucinous collagen of proliferating intima is characterized by calcium deposition. This deposition is usually more conspicuous in the presence of necrosis of atheromatous accumulations. As vascularization of calcified zones proceeds, bone and bone marrow occasionally form.

This description of intimal proliferation and degeneration has been given in

the sequence which I believe to be the common sequence. Others give different interpretations. Several contend that deposition of cholesterol and other lipids in an otherwise normal intima is the primary stimulus to intimal proliferation. There is merit in this theory, which is currently being thoroughly tested.

THE DEFINITION OF INTIMAL ARTERIOSCLEROTIC SEQUENCES IN HYPERCHOLESTEROLEMIC RABBITS

The lesions which occur in dietary hypercholesterolemic atherosclerosis in rabbits resemble some intimal atheromatous lesions in man. The lesions in the experimental animal also have features which are not encountered in the human disease. Likewise, the human disease has features which are not encountered in the experimental disease. These similarities and differences are often disregarded, leading to unjustified generalizations about the pathogenesis of human arteriosclerosis.

Apparently, the primary event in the experimental disease is an accumulation of lipids of several types in the intimal and subintimal tissues. This is followed by an accumulation of macrophages which ingest the deposits of lipids and acquire the microscopic appearance of "foam cells." Initially, local plaques of "foam cells" develop and not only encroach upon the lumen of the artery but also spread laterally to form broad confluent lesions. In time, these cells degenerate and release the accumulated lipids, which may persist in globular or crystalline form in a loose relatively acellular reticular framework. Intimal proliferation with abundant deposition of collagen, formation of elastic tissue and differentiation of proliferating cells into mature fibrocytes or smooth muscle cells, is a negligible aspect of the usual development and involution of these lesions.

In addition to the microscopic differences between intimal lesions of human arteriosclerosis and hypercholesterolemic arteriosclerosis in rabbits, there are conspicuous differences in the anatomic distribution of lesions. The intimal lesions in hypercholesterolemic rabbits, in general, appear first in the proximal aorta and spread distally. As a rule, the only major arterial branches which show severe involvement are the coronary arteries. The more peripheral arteries are rarely affected by the disease. On the other hand, the larger pulmonary arteries are consistently involved. This distribution is wholly different from that regularly encountered in human arteriosclerosis. Nevertheless, it is a very interesting distribution and an explanation of it might give some insight into reasons for vagaries of distribution of the human disease.

THE DEFINITION OF SEQUENCES IN THE VASCULAR MEDIA IN HUMAN ARTERIOSCLEROSIS

The media of arteries is nourished primarily by diffusion. As a rule, the media lies between two elastic membranes known as the internal and external elastic membranes. The aortic media is supplied with multiple similar concentric elastic membranes. The internal elastic membrane lies between the intima and the media. It is a sort of blood-media barrier composed primarily of elastic

tissue. It probably has something to do with discrimination between materials which normally pass back and forth between the cells of the (avascular) media and the blood stream. In human arteriosclerosis, the internal elastic membrane, especially of peripheral muscular arteries, often undergoes degenerative changes. These changes are multiple but the principal results are increased rigidity, calcification and fragmentation of the membrane. As these changes occur, they are often accompanied by structural modifications in the overlying intima and subjacent media. The usual intimal reaction is proliferative and basically fibrocellular in nature. The usual changes in the media are degenerative, with variable degrees of repair of degenerate structure. Whether the changes in the internal elastic membrane are responsible for modifications in the structure of the intima and media, is a question of fundamental importance. It seems probable that the loss of chemical and structural integrity of the internal elastic membrane and the subjacent media are significant early events in the development of human arteriosclerosis, especially in medium-sized arteries. At times, these events are the only ones which are recognizable microscopically.

The extreme state of lipemia and hypercholesterolemia induced in rabbits by dietary methods leads to an accumulation of lipids in many locations other than the intima of arteries. It is easy to demonstrate abnormal amounts of lipids in the media of arteries. These accumulations under ordinary experimental conditions do not seem to disturb the integrity of the media. However, when the accumulation of lipids in intimal atheromatous plaques is attended by degeneration of cell structure of the plaques, the media is often affected. The first evidence of this adverse affect is a change in the optical properties of the internal elastic membrane. This change is followed by fibrillation and development of structural discontinuities in the internal elastic membrane. As this occurs, lipids permeate the media locally and the smooth muscle cells undergo degenerative changes. These modifications are not ordinarily followed by accumulation of "foam cells" or significant signs of repair. The observed sequences and the end-result fall far short of reduplicating the customary medial degenerative and reparative changes encountered in human arteriosclerosis.

PRODUCTION IN RABBITS OF VASCULAR DISEASE RESEMBLING HUMAN ARTERIOSCLEROSIS

The preceding comments have indicated that dietary hypercholesterolemia alone does not lead to the development of a form of vascular disease generally comparable to the usual forms of human arteriosclerosis. Furthermore, a consideration of the human disease indicates that local conditions and changes in the vascular wall contribute to the development and progression of the arteriosclerotic processes.

With this in mind, a study was made of the sequences of degeneration and regeneration of arterial walls in normal rabbits (1, 2). The walls of arteries were devitalized in situ by transmural freezing. The cells of the vascular wall promptly succumbed and disappeared by lysis, without exciting an infiltration of inflammatory cells. Anatomic continuity of the residual fibro-elastic frame-

work of the frozen vascular segment persisted. Immediately following mural devitalization in continuity, intimal regeneration became apparent. The progressive proliferation and differentiation of intimal cells continued until, under perfect conditions, a new vascular wall was constructed within the degenerate shell of the once-frozen vascular segment. Within the degenerate mural shell, represented mostly by residual fibro-elastic medial structure, there was little regenerative activity. Calcium salts accumulated and as a rule were slowly resorbed or converted into bone. The residual collagen became hyalinized and the residual elastic tissue became hyalin, calcified and fragmented. These processes had many features in common with those found in human arteriosclerosis. The principal difference was the absence of large accumulations of lipids in the degenerate media or proliferated fibro-elastic intimal structure of the experimental lesions.

Therefore, the same experiment was performed in rabbits made hypercholesterolemic by dietary methods (3). This experiment showed that the sites of medial degeneration and intimal proliferation became elective sites for atheromatous localization. The lipid localization was more conspicuous in the fibro-elastic plaques of regenerated aortic intima than in similar plaques in iliac or renal arteries. Lipid localization in the degenerate media was conspicuous only in extra-aortic arterial walls, more so in renal than iliac arteries. The tendency for atheromatous localization to occur in the proliferating intima of the aorta rather than that of renal and iliac arteries, was in keeping with the natural tendency for atheromatous plaques to develop in the "normal" aortic intima of hypercholesterolemic rabbits. The tendency for atheromatous localization to occur in the degenerate media of the renal and iliac arteries was in keeping with the natural tendency for medial degeneration to develop in the coronary arteries rather than the aorta, in the control hypercholesterolemic rabbits. It seemed that the medial atheromatous localization in muscular arteries was related in some way to the occurrence of imperfections in the internal elastic membrane of the devitalized arterial wall. Multiple concentric elastic membranes of the aortic wall seemed to act as a barrier to atheromatous localization in the media.

The accumulation of lipids in the lesions was accompanied by inhibition of the processes of repair, as well as distortion of the usual regular pattern of structural arrangement, especially of regenerating intima. Furthermore, hyalin and mucinous degeneration of the newly-deposited connective tissue stroma frequently occurred in association with atheromatous deposits, especially in the regenerated intima of old animals.

This combination of complex vascular disease involving active medial degeneration, fibro-elastic intimal regeneration and atheromatous localization simulated the varied aspects of human senile athero-arteriosclerosis much more closely than did the simple atheromatous intimal disease of hypercholesterolemic rabbits. The experimental findings therefore indicated that imperfections in the media are important in arteriosclerosis. These imperfections may lead to fibro-elastic intimal proliferation, fibrosis of the media and medial calcification in normocholesterolemic animals. In the presence of an elevated blood cholesterol,

the zone of fibro-elastic intimal proliferation and the degenerate media of muscular arteries become elective sites for lipid accumulation and stromal degenerative changes without persistent calcification.

The question arises as to whether primary medial disease in the human initiates a similar sequence of events. The study of miscellaneous diseases of arteries indicates that the reaction of the human vascular wall in the presence of primary medial disease is similar to that of the experimental animal. The well known results of aortitis and arteritis due to infectious agents, allergic reactions and other causes support this conclusion. However, the nature of chronic noninflammatory progressive medial disease characterized by atrophy of smooth muscle, interstitial fibrosis and defections in elastic tissue, is still a mystery. We associate these changes with the ageing process, which in itself is no explanation. As this process exerts its influence, intimal proliferative reactions accompany it and seem to be secondary to the intramural degenerative changes. Nor can the adventitia be excluded from consideration, because changes in the adventitia may lead to medial and intimal changes. Again, this shows that imperfections in any part of the vascular wall may initiate a progression of one or another of the pathologic sequences of arteriosclerosis.

ETIOLOGY OF MURAL CHANGES IN HUMAN AND EXPERIMENTAL ARTERIOSCLEROSIS

The previous discussion has been concerned with the sequences in arteriosclerotic processes. It was implied that these sequences may be initiated or aggravated by many causes. Local trauma is at times sufficient to induce local arteriosclerotic changes. Also, it is possible to follow the sequences of arteriosclerosis as a result of inflammation of vascular walls. These inflammatory reactions may have diverse causes, such as localization of infectious agents, bacterial toxins or allergic reactions. Prolonged hypertension contributes to the development of arteriosclerosis. This is apparent in the systemic circulation but is especially impressive when hypertension involves the pulmonary arterial system. There is experimental and other evidence that excesses of certain hormones such as parathormone, adrenalin and stilbestrol may either cause or accelerate the development of arteriosclerosis. Excesses of vitamins A and D, as well as deficiencies of pyridoxine and vitamin E, may lead to special forms of arteriosclerosis. Arteriosclerotic changes may also follow the use of diets containing an excess of lipids or of cholesterol.

Other direct or contributing causes might be added. The ones mentioned are sufficiently diverse to support the belief that almost anything which is capable of producing degenerative or proliferative changes in arterial walls may cause one or another form of arteriosclerosis. Indeed, a most interesting form of arteriosclerosis follows the reduction of flow of blood as the result of a decrease in peripheral circulatory demand. This is especially conspicuous in uterine arteries during involution of the youthful uterus following a full-term pregnancy.

Despite the proof that there are many potential causes of arteriosclerosis,

there are perhaps three factors which deserve special consideration. These factors are first, the ageing process; second, hypertension; and third, the lipid composition of the blood plasma.

It is hardly necessary to mention the ageing process as a factor in arteriosclerosis. It seems self-evident. Arteriosclerosis in its common form begins in childhood and progresses throughout life, more rapidly in some than others. No one of advanced years escapes the disease. Still, the fundamental changes which are recognized as a part of the ageing process are a mystery. Microscopically, these changes are best detected in the intercellular tissues of the body, especially those intercellular tissues which are at a considerable distance from a blood supply. This is true of the principal fibro-elastic framework of the arterial wall. The maintenance of this framework and the enclosed cells depends upon acquisition of necessary nutrients and elimination of metabolites by diffusion over relatively long distances. It may be that the ageing of these supporting tissues limits the process of diffusion. This idea fits the observations better than any other. According to this idea, gradual decay of the media is due to limitation of diffusion caused by changes in the interstitial tissues. The medial degeneration then becomes primary to the proliferative and degenerative sequences characteristic of senile arteriosclerosis. But it is clear that medial degeneration alone does not always lead to these characteristic sequences. Otherwise, certain destructive medial changes such as those occurring in primary vascular amyloidosis should be accompanied by other severe arteriosclerotic changes which, in our experience, do not develop despite the chronicity and completeness of medial degeneration. Furthermore, there is no entirely consistent correlation between medial degeneration and intimal reactions in any form of human vascular disease. In this connection, it is to be emphasized that age alone, at least in experiments with rabbits, is not a factor of primary importance in the development of the degenerative and regenerative vascular lesions which we have studied (2, 3).

Profound physical changes, however, invariably occur in ageing human arterial walls. The resultant inelastic, rigid, tortuous and often dilated arteries have led many to conclude that one basic effect of the ageing process was to reduce the elasticity of elastic tissue. Our studies have shown that the elastic tissue networks of aged vessels when isolated in pure form have the same elasticity as elastic tissue of infantile vessels (4, 5). Age leads to a reduction in tensile strength, due to transverse fractures of elastic networks. It does not affect the property of elasticity, but the discontinuities in aged elastic tissue decrease the effective amount of elastic tissue. This leads to gradual dilatation and elongation of the artery. The progressive accumulation of fibrous tissue then splints the elastic tissue in an over-extended state. When this fibrous tissue is extracted by chemical methods, the elastic tissue retracts and the vessel returns to its normal youthful dimensions (5). The means by which the ageing process leads to discontinuities in elastic tissue is the important problem here.

There is good evidence that hypertension favors the development of arteriosclerosis. As a rule, the higher the diastolic pressure, the more severe the vascular

disease, especially in small arteries and arterioles. Some believe that sclerosis of arteries and arterioles precedes hypertension. This opinion is apparently justified in certain cases. It is often difficult to determine cause and effect in other cases, especially when the systemic arterial system is involved. However, the cause-and-effect relationships are clear, when pulmonary hypertension in young people with mitral stenosis definitely leads to classic severe pulmonary arteriosclerosis.

The mechanism by which intravascular hypertension causes or accelerates the development of arteriosclerosis is unknown. It seems that the increased tension excites a reaction of the tissue of the vascular wall to undue stresses which it was not initially designed to withstand. This imbalance between structure and stress often arises in consideration of factors, especially local ones, which govern the development of arteriosclerosis. If this imbalance is important, the mechanism by which proliferative and degenerative vascular reactions are mediated by the imbalance is also important. Nothing is known about this but, with hypertension, the sequences and character of the reactions in large arteries are essentially the same as those which occur in the absence of hypertension. It should be remembered, however, that hypertension is a relative term. We should not think of hypertension as an arbitrary range of elevated blood pressure. *We should regard hypertension as a range of blood pressure which is elevated with respect to the tolerances of different segments of normal and abnormal vascular walls. The vascular wall, and not the mercury manometer, is the critical judge of hypertension.*

The idea that the quantity and physical state of plasma lipids are important causes of arteriosclerosis, is attracting attention today. Deposits of lipids, rich in cholesterol, appear at about 10 years of age in the intima of the human aorta. These fatty plaques may gradually enlarge and coalesce with advancing years, or undergo degeneration and resorption. Some believe that the sequences of regenerative and degenerative arteriosclerotic changes are initiated by the effects produced by these lipid deposits in the intima.

The principal argument among pathologists is whether the fatty deposits are primary or secondary events in the development of arteriosclerosis. The discovery that, in rabbits maintained on a diet rich in cholesterol, severe atherosclerosis developed, gave impetus to the idea that hypercholesterolemia alone was responsible. The development and regression of these plaques was studied in the experimental animal but the full picture of the human disease, especially the intimal proliferative and medial degenerative aspects, was not encountered. In order to obtain these effects, it was necessary to produce some experimental imperfection in the arterial wall. Once this was done, the lesions resembled those commonly found in human arteriosclerosis (3). Localization of lipids at sites of medial injury and intimal proliferation was demonstrated. The findings seemed to favor the concept of a secondary but nevertheless important role for the lipids.

Meanwhile, it was shown that certain protein-lipid complexes could be isolated from animal and human plasma by centrifugation. These fractions had certain sedimentation constants. Then, lipo-protein complexes with character-

istic physical properties were found in the plasma of hypercholesterolemic rabbits and humans with severe arteriosclerosis. The amount of the lipo-protein which was found was not related quantitatively to the level of the plasma cholesterol. Emphasis was then placed upon the idea that abnormal plasma lipo-protein complexes represented a deviation in metabolism manifested by the production of chemical compounds which circulated in the blood, accumulated in the intima of arteries and initiated arteriosclerotic sequences. This is a very attractive theory which is yet to be fully judged, as evidence for and against it slowly accumulates. In view of the over-all picture of human and experimental arteriosclerosis, it is doubtful that any single cause or aggravating factor will be sufficient to explain the complexities of the process.

CONCLUSIONS

The principal structural changes encountered in the common forms of senile human arteriosclerosis can be reproduced in the experimental animal. The most satisfactory reproduction requires the induction of hypercholesterolemia in animals with defects in the vascular wall that lead to active medial degeneration and intimal proliferation. It may be concluded from the observations that further approach to an understanding of the human disease by use of experimental animals might profitably involve a study of vascular degenerative and reparative sequences in the presence of appropriate dynamic and chemical imbalances between the vascular wall and its immediate environment.

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LEFT VENTRICULAR FAILURE AND ACUTE PULMONARY EDEMA

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Acute pulmonary edema has been attributed to left ventricular failure ever since the experimental study of Welch in 1878. In recent years, the terms have become synonymous, so that in many hospitals acute pulmonary edema is not even listed as a separate clinical entity. However, it should be kept in mind that, although left ventricular failure may (or may not) cause pulmonary edema, acute pulmonary edema may not be due to left ventricular failure. Therefore, a detailed study of the causes and mechanism of pulmonary edema is necessary in order to define its relationship to changes of cardiac function.

LEFT VENTRICULAR FAILURE AND LEFT VENTRICULAR STRAIN

Left ventricular failure has been defined as: (a) the inability of the left ventricle to forward all the blood received from the pulmonary circulation; or (b) the inability of the left ventricle to supply enough oxygen to the tissues of the various organs.

The first definition considers only "backward failure" or congestion of the lungs; the second considers only "forward failure" or depletion of the periphery, which is followed by anoxia of the tissues. Both are probably taking place at the same time but congestion of the lungs is more easily detected than arterial depletion or decrease of cardiac output, because compensatory reflexes may keep blood pressure at a normal level so that anoxia is taking place only in certain vascular districts.

Left ventricular failure may cause either the syndrome of shock or that of acute pulmonary edema. It may be followed by right ventricular failure, with the complete picture of congestive failure.

Left ventricular failure is necessarily of brief duration. In normal conditions, both ventricles have the same output. A different output may take place only through 1) modification of the residual blood within the ventricles themselves, or 2) through displacement of blood from the lungs to the periphery or from the periphery to the lungs. With a heart rate of 60 and an output of 60 cc., if the left ventricle is forwarding 1 cc. less than the right, a volume of 600 cc. is left behind in ten minutes, causing a tremendous increase of pulmonary pressure.

Even if sudden and of brief duration, left ventricular failure is frequently preceded by a long period of *left ventricular strain*, which can be defined as a decreased reserve of the left ventricle.

Left ventricular reserve may decrease in two ways: (a) through increase of the average work, as in aortic valvular disease, arterial hypertension or patent

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ductus; or (b) through decrease of the efficiency of the pump, as in myocarditis or coronary heart disease.

In the first category, the reserve is reduced from below (increase of habitual work), whereas in the second the reserve is reduced from above (limitation of maximal work).

Direct proof of left ventricular failure can be obtained in two ways: (a) By means of radiocardiography.[2] A radioisotope is injected into a vein. A Geiger counter applied over the precordium reveals that the isotope, instead of being rapidly eliminated, stays within the left ventricle for a long time, due to an increase of the residual blood within the left ventricle. (b) By means of left heart catheterization.[3] This procedure is based on the introduction of a catheter through an artery until it reaches the left ventricle. Left ventricular failure is revealed by an increase of diastolic pressure.[4]

Indirect evidence of left ventricular failure may be found: (a) if right heart catheterization reveals an increase of the systolic but not of the diastolic pressure of the right ventricle (structural lesions of the cardiac valves, the pulmonary vessels and the pericardium must be excluded); (b) if roentgenologic examination reveals sudden enlargement of the left ventricle without enlargement of the right.

Left ventricular strain is more easily detected. It is usually accompanied by long-lasting dilatation and hypertrophy of the left ventricle, as revealed by palpation, percussion and roentgenology. It is frequently accompanied by an increase of either the systolic or the mean pressure in the pulmonary arterial circulation.[5] It is frequently revealed by auscultatory and phonocardiographic data, such as gallop rhythm, loud second pulmonic sound, or a systolic murmur at the apex or over the pulmonic area. It may be revealed by pulsus alternans. Also, certain electrocardiographic signs are the result of hypertrophy of the left ventricle and of left ventricular strain (in a clinical sense). These signs are: left axis shift; delay of the intrinsicoid deflection in the chest leads V5-V6; inversion of T in leads 1, VL, and V5-V6.

ACUTE PULMONARY EDEMA

Acute pulmonary edema is encountered in a variety of conditions. Some of these conditions involve left ventricular failure or strain, whereas others seem to be entirely different (3).

As shown in Table 1, acute pulmonary edema is chiefly found: (a) in cardiac conditions with left ventricular strain, (b) in mitral stenosis, (c) in neurologic conditions, and (d) in lesions of the respiratory system.

[2] The normal radiocardiogram, according to Prinzmetal (1), consists of two waves the R and the L waves. The R wave is due to passing of the isotope through the right ventricle; the L wave is due to its passing through the left ventricle. Studies of the author (2) have confirmed this finding, both in animals and patients.

[3] This procedure should not be resorted to because of the hazards involved.

[4] Diastolic pressure of a healthy left ventricle is zero.

[5] An exception is that of aortic stenosis where the strain of the left ventricle may be accompanied by normal or low blood pressure.

Evaluation of the mechanism of acute pulmonary edema cannot be attempted without reference to experimental studies.

TABLE 1

Conditions Associated with Acute Pulmonary Edema

A. Diseases of heart and vessels	Luetic heart disease (aortic insufficiency, aortitis, aortic aneurysm). Rheumatic heart disease (mitral insufficiency or stenosis, aortic insufficiency). Coronary heart disease (especially coronary occlusion). Hypertensive heart disease (essential or secondary hypertension; uremia). Congenital heart disease (coarctation of aorta). Shock.
B. Diseases or lesions of central nervous system	Trauma to the skull. Subarachnoid hemorrhage. Cerebral hemorrhage, embolism, thrombosis, or abscess. Encephalitis, meningitis, poliomyelitis, tetanus.
C. Diseases or lesions of respiratory system	Pneumonia, drowning, strangulation. Inhalation of irritant or toxic gases. Pulmonary embolism (rare). Thoracentesis. Trauma to the chest.
D. Allergy	Angioneurotic edema. Serum sickness. Injections of gold preparations.
E. Miscellaneous	Thyroid crises. Beri-beri heart disease.
F. Stimulation of hollow viscera	Distention of esophagus, stomach, or gall bladder. Emptying of distended bladder.
G. Surgical and obstetrical cases	Pregnancy, especially in cases with mitral lesions or eclampsia. Following transfusions or infusions, especially in surgical, anemic or cardiac patients. After manipulation of stellate ganglia.
H. Toxic pulmonary edema	Thiourea, iodides, muscarine, eserine, methylsalicylate.

TABLE 2

Experimental Pulmonary Edema

Ligation of aortic arch (rabbit)	Welch (4).
I.v. injection of epinephrine (rabbit)	Meltzer (5), Auer and Gates (6), Luisada (7, 30) McKay and Pecka (8), Halpern *et al.* (9).
Injection of silver nitrate or alcohol into the ventricular walls (dog)	Coelho and Rocheta (10), Cataldi (11).
Rapid intravenous or intracarotid infusions (dog)	Cohnheim (12), Luisada and Sarnoff (13), Luisada and Contro (14).
Vagotomy (rabbit, guinea pig)	Frey (15), Farber (16).
Suboccipital injection of veratrin or fibrinogen plus thrombin; or trauma to the brain (rat, rabbit, dog)	Jarisch *et al.* (17), Cameron and Kuo (18), Sarnoff and Sarnoff (19), McKay (20), Harrison and Liebow (21).
Ingestion of ammonium chloride (guinea pig)	Koenig and Koenig (22), McKay *et al.* (23), Cameron and Sheikh (24).
Injection of various poisons (rabbit, dog)	Sahli (25), Teissier and Guinard (26).
Hypoglycemia	McKay and Pecka (27).
Left ventricular strain plus epinephrine or CNS stimulation.	Paine *et al.* (28).

Experimental pulmonary edema has been induced by numerous procedures (Table 2). Several of these methods, and especially the last one listed in the table reproduce conditions existing in clinical cases. Therefore, certain conclusions

concerning the mechanism and therapy of experimental pulmonary edema can be extended to clinical pulmonary edema.

Three main factors favor pulmonary edema: (a) *High pressure in the pulmonary capillaries.* This is usually the result of forceful cardiac dynamics, with either increase of peripheral resistance and normal venous return, or increase of venous return and normal or increased peripheral resistance. In particular, it should be kept in mind that a sudden and violent peripheral vasoconstriction leads to displacement of a large mass of blood from the periphery and the portal circulation to the lungs. In the presence of decreased reserve of the left ventricle or obstruction (as in mitral stenosis), this may result in acute edema. (b) *Increased permeability of the pulmonary vessels.* This may be favored by allergy, poisons, anoxia, or severe dyspnea (suction effect). (c) *Decreased osmotic pressure of the blood.* This is encountered after prolonged saline infusions, in lipoid nephrosis, starvation, or diseases of the liver. However, the effect of this factor is widespread, and causes pulmonary edema only in the presence of edema of other organs.

Among the conclusions reached by experimental workers, the following are important: (a) Extreme stimulation of the brain or of the carotid body leads to direct or reflex stimulation of the sympathetic system, followed by severe vasoconstriction. This leads to: increased peripheral resistance with increased load of the left ventricle; displacement of a large mass of blood from the arterioles, capillaries, and blood reservoirs towards the veins; increased venous return; and finally, filling of the lungs with a great mass of blood. In other words, this neurologic stimulation causes increased output of the right ventricle, increased pressure in the pulmonary capillaries, and at the same time, increased difficulty in the emptying of the left ventricle. This mechanism leads to pulmonary edema only if conditions are extremely severe; it may be an important factor if left ventricular strain is present, and even more so if there is already left ventricular failure. (b) Stimulation of carotid-body receptors causes a dilatation of the pulmonary arterioles (29). Increased output of the right ventricle plus dilatation of the pulmonary arterioles increases the pressure in the pulmonary capillaries and favors edema. A similar vasodilatation probably takes place in various other conditions involving stimulation of the sympathetic system.

The following considerations may explain the various types of pulmonary edema:

A. Clinical pulmonary edema following trauma to or lesions of the central nervous system, experimental pulmonary edema following intracisternal injection of irritating substances, or edema following poisoning with ammonium salts. In these types, there is severe sympathetic stimulation. While this stimulation causes vasoconstriction and increased resistance, with a severe load placed on emptying of the left ventricle, it also causes redistribution of blood and its accumulation in the lungs. Even if the heart is normal, this redistribution of blood plus the strain placed on the left ventricle, may cause pulmonary edema.

B. Mitral stenosis. Here, the outflow of blood from the lungs is impeded, even in the resting state. Sympathetic stimulation, caused by excitement, exertion, exposure to cold, anger or fright, is followed by two phenomena: on

one hand, tachycardia, which shortens diastole and impairs emptying of the left atrium; on the other hand, vasoconstriction and redistribution of the blood, with accumulation in the lungs.

C. Clinical pulmonary edema of patients 1) with hypertension, aortic insufficiency, or aortic stenosis, 2) following minor coronary attacks, and 3) following transfusions in surgical, obstetrical or cardiac cases. Experimental pulmonary edema of the dog following 1) damage to the aortic valve plus administration of adrenalin, or cerebral embolism, and 2) rapid intracarotid infusion; and of the rabbit following 1) adrenalin administration, and 2) ligation of the aortic arch. In these conditions there is left ventricular strain with increase of left atrial and pulmonary venous pressures. Excitement and exposure to cold or exertion in clinical cases, and direct or reflex sympathetic stimulation in the experimental types, cause redistribution of the blood, with accumulation in the lungs and acute pulmonary edema. The increased peripheral resistance may transform the ventricular strain into ventricular failure.

D. Clinical pulmonary edema of massive myocardial infarction; and experimental pulmonary edema following injection of silver nitrate into the ventricular wall. Under these circumstances, the power of the left ventricle is decreased. This leads to a marked increase of pulmonary capillary pressure, only if an adequate venous return is maintained. Therefore, severe (but not too severe) lesions of the ventricle are the most effective. A peripheral mechanism caused by cerebral ischemia, carotid-sinus hypotension, or carotid-body hypoxia, may contribute to the disturbance by causing peripheral vasoconstriction. The accumulation of blood in the lungs seems to be due to both a cardiac and a vascular mechanism.

E. Clinical or experimental pulmonary edema of phosgene inhalation, drowning, strangulation, pneumonia, or chronic congestive failure. In these conditions direct damage to the capillary wall and the action of hypoxia on the pulmonary capillaries are the most important factors, probably through liberation of histamine. The cerebral and carotid hypoxia may contribute, by causing reflex vasoconstriction.

TREATMENT

Treatment of left ventricular failure

On account of the brief duration of this condition compatible with life, its therapy should be *preventive*. In this respect, most of the accepted procedures maintain all their value. They include digitalis, mercurial diuretics, salt-poor diet, xanthines, and sedatives. Exposure to cold, excitement, and excessive exertion, should be avoided. Among the sedatives, chloral hydrate (1 Gm. orally or by rectum) at bedtime, has frequently a beneficial action. Supper should be a small meal and at least three hours should elapse thereafter, before retiring.

Sympatholytic drugs (dibenamine, hydergine) have not been tried in clinical cases so far, but deserve a careful clinical trial. In extreme hypertension, sympathectomy may prevent recurrent pulmonary edema, as observed by the author.

Treatment of acute pulmonary edema

A. *Pharmacologic treatment of the attack.* This may require a large number of drugs. Some of them, however, have numerous contraindications, as shown in Table 3.

TABLE 3

Pharmacologic Treatment of Pulmonary Edema

Treatment	Indication	Contraindication	Mechanism of action
Atropine (31) (s.c., i.v.)	Coronary occlusion; lesion of CNS	All other cases	Doubtful
Morphine (7, 31) (s.c., i.v.)	Hypertension; heart failure; coronary occlusion	Allergy; shock; toxic gases; pregnancy; drowning; neurologic conditions	Decreased venous return; slower respiration.
Phenobarbital (7, 31) (oral, i.v.)	Same	Same	Central sedation; decreased venous return?
Chloral hydrate (7, 31) (rectal, oral, i.v.)	Same	Same	Same
Mercurials (i.v.)	Same	Same	Decreased venous return.
Strophanthin-Digoxin-Digitoxin (i.v.)	Heart failure	Mitral stenosis; coronary occlusion; shock; toxic gases	Increased myocardial efficiency; primary & secondary decreased venous return.
Sympatholytics (14) (i.v.)	Hypertension	Same	Decreased peripheral resistance; also decreased pulmonary vasodilatation.
Spinal anesthesia (32)	Same	Same	Decreased peripheral resistance
Aminophyllin (i.v.)	Same	Same	Decreased peripheral resistance
Antihistaminics (33)	All cases, especially allergy	—	Decreased permeability
Heparin (14)	All cases	—	Same

The sympatholytic drugs (dibenamine and hydergine) and heparin have been tried, so far, only in experimental pulmonary edema. Their remarkable action warrants a clinical trial.

B. *Physical or physico-chemical treatment.* This is indicated in Table 4.

Alcohol-oxygen vapor therapy, which utilizes the antifoaming action of alcohol, was first tried successfully in animal experiments; then it was applied to clinical cases. The latest reports (34, 38), including those on patients with severe pulmonary edema who did not receive other forms of treatment, have definitely proved the usefulness of this method.

Because a precise etiologic diagnosis is not always immediately possible, the

following plan of treatment should be used: (a) Alcohol-vapor therapy should be started as soon as possible (by nasal catheter, using 95 per cent alcohol, in conscious patients; by mask, using 40 per cent alcohol, in unconscious patients). Oxygen is started, with the flow regulated at 3 liters per minute; the flow is increased gradually up to 10 liters within the first ten or fifteen minutes. In the meantime, pulse, blood pressure, auscultation of the heart, a brief history, and an electrocardiogram, should give a better perspective of the case, so that within the first twenty minutes, an adequate and precise pharmacologic or physical therapy may be started. According to the etiology of the case, atropine, morphine, phenobarbital, sympatholytic drugs, heparin, or other procedures should be used. In many instances these will not be necessary, simply because the attack is already decreasing in severity because of the effect of alcohol therapy.

TABLE 4

Physical or Physico-chemical Treatment of Pulmonary Edema

Treatment	Indication	Contraindication	Mechanism of action
Hot bath	Hypertension	All other cases	Vasodilatation; decreased venous return & decreased arterial resistance.
Venesection; application of tourniquets.	Hypertension (mitral stenosis)	All other cases	Decreased venous return.
Oxygen (inhalation)	All cases	—	Decreased anoxia.
Pressure (35) respiration	Most cases	Shock	Resistance to transudation; decreased venous return.
Alcohol (35–38) (inhalation)	All cases	—	Changes in surface tension; decrease of foam; less anoxia; mild central sedation.

However, protracted pulmonary edema is not unusual. In such severe cases, alcohol therapy is continued as long as necessary (even for twelve hours), with brief intervals of rest, in addition to the other procedures.

SUMMARY

1. Left ventricular failure and left ventricular strain are defined. Physical and technical aids to diagnosis are given.

2. Acute pulmonary edema may be associated with a variety of conditions (cardiac, neurologic, and other), which may include left ventricular strain and may or may not include left ventricular failure.

3. Experimental pulmonary edema may be induced in several ways, and the resultant data contribute to the understanding of this syndrome.

4. The main factors in pulmonary edema are listed, and the mechanism of this clinical syndrome is discussed. The factors vary in importance, according to the etiology of the edema and other favoring elements.

5. The treatment of left ventricular failure is indicated.

6. The treatment of pulmonary edema is discussed. It is based on the action of drugs on procedures utilizing physical and physico-chemical means, or both.

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ARTERIOSCLEROTIC ANEURYSM OF THE POPLITEAL ARTERY

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Arterial aneurysms have been objects of medical curiosity for many centuries (1, 2). Undoubtedly aneurysms of the popliteal artery were among the first to be known to medical science because of their anatomic accessibility and also because, next to the aorta, the popliteal artery is the commonest site of aneurysm. Almost all of the aneurysms of the popliteal artery observed in recent years have been caused by arteriosclerosis.

As the number of older persons in our population increases, so will the incidence of arteriosclerotic popliteal aneurysm. This increased incidence, plus the recent advances in anesthesiology and surgery that have made surgical treatment of peripheral aneurysms much less hazardous for patients in the older age groups, has been responsible for the recent revival of interest in this subject.

In 1940 Harley (3) reviewed 35 cases of popliteal aneurysm and in 1949 Linton (4) reported 42 cases, in 14 of which he used surgical treatment. The patients having popliteal aneurysm are predominantly men more than 50 years of age.

Follow-up data on 69 patients having 100 popliteal aneurysms seen at the Mayo Clinic were reported recently by us (5). In our series, 66 of the 69 patients were men and the average age at the time of diagnosis was 63 years. Aneurysms of the popliteal artery are frequently bilateral. This was true in 31 of our 69 patients.

ETIOLOGY

The commonest cause of aneurysm of the popliteal artery is arteriosclerosis. Ninety-six per cent of the aneurysms in our series and 74 per cent in Linton's series were arteriosclerotic in origin. Although sporadic cases have been reported in which popliteal aneurysm is attributed to syphilis (6–10), the diagnosis, as a rule, has not been confirmed pathologically. The only aneurysm in our series which was pathologically characteristic of syphilis also showed arteriosclerotic changes (Table 1).

Several authors have stressed the importance of trauma as a contributing factor to the development of popliteal aneurysm (3, 11–14). We were not impressed with this factor in our series. The only traumatic aneurysm which we encountered was in a boy, 17 years old, who had sustained a gunshot wound in the popliteal space. There must be, however, some explanation for the fact that there are so many arteriosclerotic popliteal arteries, but so few aneurysms develop.

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ASSOCIATED DISEASES

Hypertension and the various manifestations of atherosclerosis frequently coexist with popliteal aneurysm (Table 2). We have no explanation for the low incidence of diabetes mellitus in our group of patients who were suffering from a disease that is predominantly arteriosclerotic in nature. Multiple aneurysms, both popliteal and extrapopliteal, were common in this group. The sites of extrapopliteal aneurysms found in these patients are listed in Table 3.

TABLE 1

Etiology of 100 popliteal aneurysms

Etiologic factors	Aneurysms		
	Total	Clinical diagnosis only	Pathologic diagnosis
Arteriosclerosis	92	71	21
Syphilis	3	3	0
Arteriosclerosis and mycosis*	1	0	1
Arteriosclerosis and syphilis	3	2	1
Trauma	1	1	0

* Brucella cultured from wall of aneurysm.

TABLE 2

Coexisting or associated diseases in 69 patients with popliteal aneurysm

Disease	Patients
Diabetes mellitus	1
Hypertension (blood pressure more than 160/90 mm. Hg)	41
Angina pectoris or myocardial infarction	16
Cerebrovascular accident	10
Thromboangiitis obliterans	2
Arteriosclerosis obliterans	53
Syphilis (positive serologic reaction)	6
Multiple aneurysms*	40
Extrapopliteal aneurysms	17

* Includes 31 patients with bilateral popliteal aneurysms.

SYMPTOMATOLOGY

Until complications occur, most aneurysms of the popliteal artery are asymptomatic. Frequently the patient or his alert physician discovers the pulsatile mass behind the knee.

Local pain, swelling and an increase in the prominence of the venous pattern of the leg below the knee do not appear until the aneurysm has become large enough to cause pressure on the popliteal vein and nerve. Symptoms of ischemia, such as intermittent claudication, ischemic neuritis, ulceration and gangrene, occur when the aneurysm becomes occluded by a thrombus or when peripheral embolization occurs from a mural thrombus within the aneurysm.

Since arteriosclerosis obliterans is frequently seen in patients with popliteal aneurysms, it is not uncommon to find ischemic neuritis and intermittent claudication in a leg distal to a popliteal aneurysm which is pulsating normally, although the arterial pulsations of the foot are absent. In such instances arteriosclerosis obliterans distal to the aneurysm is the cause of these symptoms and the aneurysm is an incidental finding, unless it can be determined that peripheral embolization from a mural thrombus within the aneurysm has led to the occlusion of the peripheral arteries. Embolic occlusions of this nature usually produce symptoms suddenly, whereas arteriosclerosis obliterans is a more gradually progressing process.

DIAGNOSIS

In the diagnosis of no other disease is physical examination more important than in aneurysm of the popliteal artery. In 98 of our 100 aneurysms, the diagnosis was made by careful inspection and palpation of the popliteal space. The finding of a thrill and bruit over the aneurysm is inconstant and not essential to the diagnosis.

TABLE 3

Sites of 24 extrapopliteal aneurysms in 17 patients with popliteal aneurysms

Location of aneurysm	Aneurysms
Abdominal aorta	8
Femoral artery	9
Iliac artery	4
Thoracic aorta	2
Dorsalis pedis artery	1

Aneurysms that are not occluded by a thrombus are felt as pulsating masses in the course of the popliteal artery. They may be well localized or diffuse and they vary in size from little larger than a walnut to the size of a grapefruit or larger.

Aneurysms that are occluded by a thrombus are felt as firm, often rather hard, nonpulsatile masses in the popliteal space. They are usually somewhat movable. Aneurysms, whether occluded or open, are usually not tender to palpation.

Aneurysms cast a shadow on plain roentgenograms of the popliteal area in only about half of the cases. Although a frequent occurrence, calcification in the wall need not be present to make the aneurysmal mass visible on a plain roentgenogram.

Arteriography is a valuable procedure in confirming the clinical diagnosis of popliteal aneurysm and in delineating its magnitude for the surgeon but it is not a substitute for physical examination.

In the differential diagnosis, all masses of the popliteal space must be considered. These include benign tumors, such as lipomas and fibromas, synovial herniations (Baker's cysts) and spontaneous or traumatic hematomas. Although the finding of pulsation is helpful, it must be remembered that aneurysms

occluded by a thrombus do not pulsate and a mass overlying a normal popliteal artery may give the impression of a pulsating tumor.

Special consideration must be given to arteriovenous fistula and false aneurysms of the popliteal space in the differential diagnosis. In the former there is invariably a history of a penetrating wound except in the rare instance of congenital fistula, in which case there are usually multiple fistulas. In addition to a pulsating mass a continuous thrill and bruit are present over the area, the prominence of the venous pattern is increased and local heat is often increased. Compression of the femoral artery proximal to the fistula is often followed by slowing of the heart rate (Branham's sign). In the last analysis arteriography will differentiate true aneurysm from arteriovenous fistula.

False aneurysms of the popliteal artery result usually from rupture of a true aneurysm, although spontaneous or traumatic rupture of an otherwise normal artery may result in a false aneurysm. Oftentimes only the pathologist can differentiate between true and false aneurysms, for in the latter the wall of the aneurysm is formed from organized blood clot. Clinically and arteriographically

TABLE 4

Summary of 121 complications of 62 popliteal aneurysms

Complication	Occurrences
Acute arterial occlusion (thrombosis or embolus)	45
Gangrene	24
Pressure on veins	24
Rupture	16
Pressure on nerves	12

it is impossible to distinguish between the two, but this is of little importance since the treatment is no different.

COMPLICATIONS

The complications of popliteal aneurysm, to which we have already alluded, are frequent and often disastrous, to the point of costing the patient his limb or his life. Complications often appear suddenly and without warning and may be the first indication to the patient and his physician that an aneurysm is present.

The common complications of popliteal aneurysm and the frequency with which they occurred in our series are listed in Table 4. Once an aneurysm has caused one complication, others seem more prone to develop.

PROGNOSIS

The prognosis in cases of popliteal aneurysm is at best uncertain. Linton (4) reported on 22 limbs with popliteal aneurysms, in 50 per cent of which gangrene was present when the patients were admitted to the hospital. He added that gangrene developed in an additional 27 per cent of the limbs while the patients were in the hospital. All of these (77 per cent) required amputation.

In our series of 100 popliteal aneurysms, 49 were complicated at the time the

patients were first seen at the clinic. Thirteen of the 51 originally uncomplicated aneurysms became complicated subsequent to the time that the patients were first seen at the clinic. Many of the aneurysms had more than one complication. The incidence of subsequent complications undoubtedly would have been much higher if all of the patients had been followed throughout the rest of their lives.

Twenty of the 100 aneurysms led to amputation of the limbs, either at the initial visit to the clinic or subsequently. Of these 20 amputations, 18 were performed for the group of 80 aneurysms for which immediate surgical correction was not undertaken. This is a mortality rate for limbs of roughly 23 per cent. This figure is bound to increase as the rather short follow-up time on these patients increases. The majority of the amputations were performed for gangrene secondary to sudden occlusion of the aneurysm itself by a thrombus, or occlusion of a distal artery by an embolus arising from a mural thrombus within the aneurysm.

Popliteal aneurysms that carry the worst prognosis are those that have given rise to an embolus or emboli—the limb having temporarily recovered. Also carrying a serious prognosis are aneurysms which are leaking or have enlarged to the point of causing pressure on the neighboring vein or nerve. In our series there were 11 aneurysms that had caused one or more of these complications previous to the time that diagnosis was first made at the clinic. Five (45 per cent) of these led to amputation of the limb subsequently, most of them within a year. These amputations were due to subsequent complications which, as said before, are particularly prone to develop once an aneurysm has caused its first complication.

Acute occlusion of a popliteal aneurysm by a thrombus has frequently been referred to in the literature as a "spontaneous cure" (15–18). It is true that if a limb survives for three months after such an acute arterial occlusion, further complications from the aneurysm are unlikely, but the resultant ischemia of the lower part of the leg and foot is likely to be a severe handicap.

In our series acute occlusions of the popliteal aneurysms occurred in 24 instances. Eight (33 per cent) resulted in amputation of the limb within three months of the acute episode. Of the 16 surviving limbs, only 4 (17 per cent of the original 24) became asymptomatic, useful extremities. "Spontaneous cure" of popliteal aneurysms by thrombosis, therefore, involves a high risk of mortality for the limbs, and of morbidity. Certainly this type of management is not desirable.

The serious prognosis in popliteal aneurysm is not limited to the limb which harbors it. Thirty-two of the 69 patients in our series died during the period of follow-up and 6 of the deaths could be directly attributed to complications caused by the aneurysm. All 6 patients had toxemia from gangrene. Three died immediately after amputation of the gangrenous extremity.

TREATMENT

Surgical treatment has been the only satisfactory method of dealing with aneurysms of the popliteal artery and of thwarting the serious complications

they so frequently cause. That such treatment is not without danger is shown by the fact that the incidence of postoperative gangrene has been estimated at 5 to 15 per cent (19). Matas (20) reported that postoperative gangrene occurred in 5 per cent of his patients. In our series 26 aneurysms were treated surgically, 23 of the operations being performed by surgeons from the clinic. There were no operative deaths. There were only 2 instances of postoperative gangrene; both occurred within ten days of operation and amputation was required for both. In both of these instances the aneurysm was enlarging so rapidly that the distal circulation was severely compromised and the legs were severely ischemic preoperatively. The operations were performed as an emergency alternative to amputation in a desperate effort to salvage the limb.

Matas (20) has reported good results from surgical treatment in 93 per cent of his patients. We have classified our results as excellent in 83 per cent of the cases we have been able to follow adequately. This means that the limb is entirely asymptomatic and useful in every respect. It is not unusual for patients to complain of swelling, pain and intermittent claudication in the affected extremity for a few months after operation but these symptoms almost invariably disappear.

Several types of operative procedures have been advocated. Ideally, it would be desirable to restore continuity of the artery by the procedure of reconstructive endo-aneurysmorrhaphy as advocated by Matas (20, 21) or by the use of a vein graft as advocated by Blakemore (22). Practically, however, the shape of the aneurysm and the condition of the wall of the involved artery only rarely lend themselves to these procedures. In most instances it is necessary to interrupt the continuity of the artery and to depend on the collateral circulation to maintain adequate circulation to the leg.

In obliterative endo-aneurysmorrhaphy (20, 21), the lumen of the aneurysm is obliterated, but the aneurysm itself is not removed.

The current procedure of choice is total extirpation of the aneurysm as reintroduced by Ranschoff (1). Recently prophylactic lumbar sympathectomy has been performed to insure maximal collateral circulation before the aneurysm is extirpated (4, 23, 24). Linton (4) preferred sympathectomy several days before the extirpation, whereas MacCarty, Janes and Allen (25) recommended that the two procedures be carried out under one period of anesthesia. Linton has reported on 14 patients in whom the combined procedure was attempted. In 13 it was successful. One patient died before the aneurysmectomy was undertaken. Janes and Ivins (23) have reported 9 consecutive cases in which the combined procedure was successful. One of these was a man, 81 years old, who obtained a satisfactory result from extirpation of a popliteal aneurysm after preliminary lumbar sympathectomy.

SUMMARY AND CONCLUSIONS

Aneurysms of the popliteal artery are predominantly arteriosclerotic in origin and, therefore, occur most frequently in patients who are 50 or more years old. They occur preponderantly in males.

Aneurysms of the popliteal artery usually do not cause symptoms until complications develop. Diagnosis depends on careful palpation of the popliteal space and this should be an integral part of every physical examination in middle-aged or elderly patients, regardless of whether or not there is any historical evidence of occlusive arterial disease.

Popliteal aneurysms are prone to have serious complications that can lead frequently to amputation of the limbs that harbor them. For this reason surgical treatment of popliteal aneurysm is advocated for any patient whose general condition permits it. After complications develop, the risk of surgical treatment is higher, but the risk of conservative treatment is also higher; our data indicate that the incidence of subsequent amputation is about three times as great in limbs with popliteal aneurysms that are not treated surgically. The surgical procedure of choice is extirpation of the aneurysm after lumbar sympathectomy has been performed.

The astute physician can do his patient a great service by early diagnosis and prompt institution of surgical treatment of arteriosclerotic popliteal aneurysms, preferably before complications develop.

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THE CYTOLOGIC SMEAR IN GYNECOLOGIC GERIATRIC PRACTICE

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Gynecologic cancer, of which the uterine variety is by far the most common, kills more women than does any other type of female cancer. Although cervical carcinoma frequently occurs in the younger woman (approximately 30 per cent of our series being found in patients 40 years of age or younger (1)), gynecologic cancer in the main is a disease of the older female. Especially is this true of corpus and vulval carcinoma. Of the more recent methods in use for early diagnosis, the Papanicolaou smear has shown the most promise and it is this method we plan to discuss here. Certainly the delay periods in pelvic cancer (2) are discouraging enough to warrant its use in more cases. The value of the test in nonmalignant conditions of the female genital tract will also be considered.

The effects of aging on the vaginal smear

Termination of the reproductive period with cessation of ovarian activity affects the whole body, and the vagina and the vaginal smear share in these changes. During life the thickness of the vaginal epithelium depends primarily on the amount of estrogenic hormone available. At birth this hormone is present in excessive amounts from the maternal dowry which reaches the fetus through the placenta. In the young female child the epithelium thins, but with puberty the epithelium again thickens and reaches its maximum during pregnancy. With the menopause, thinning again appears, being apparently due to the added factor of aging of the vaginal epithelium. All these changes are significant in that the vaginal smear, barring the presence of infection, shows an increase in superficial cells with acidophilic staining and small dense nuclei, and occasionally reveals completely cornified cells, in association with higher estrogen levels. In general, the farther the woman is from the menopause, the less striking is this estrogen effect. Varying degrees of deficiency are characterized by round and ovoid basal cells and leukocytes. The previous regular cyclic variations also disappear. However, it is well known that the menopause is not followed, unless artificially induced by radiation or surgery, by sudden lack of estrogenic effect. Instead there is a gradual and sometimes irregular waning of estrogenic activity with some of the estrogen being probably of adrenal origin. It is believed, too, that the "pressure" of residual postmenopausal estrogen may be of etiologic significance in corpus carcinoma (3). On the whole, there is little correlation between the severity of the menopausal syndrome and the status of the vaginal smear (4).

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Aside from familiarity with vaginal changes it is necessary also to be familiar with the normal cytology of the cervix and the endometrium. These cells, especially the endometrial, are usually absent in the normal postmenopausal smear.

Techniques

Our routine consists of taking at least three smears from the genital tract (5). These consists of: a) vaginal (aspirated from the posterior fornix), b) cervical (scraped from the portio with a wooden spatula), and c) endocervical and endometrial (aspirated with the use of a laryngeal-type metal cannula from the endocervix). Vulvar smears are obtained by merely rubbing or scraping the lesion of the vulva.

The material thus collected is put on clean slides, appropriately labeled, and *before the smear can dry*, placed in a Coplin jar containing equal parts of 95 per cent alcohol and ether. Fixation is accomplished in a few minutes; if necessary, the slides may be kept in fixative for a week or two before staining. In our opinion the best staining method is that formulated by Papanicolaou (6).

It is important to remember that the instruments used in taking this smear must be dry, and that the patient should not have taken a douche for at least a day. These precautions are necessary, since water alters cellular detail and a douche mechanically washes away accumulated cells. The smear should not be too thick and when spread on the slide should be thinned out gently so as not to distort the cells. If the secretions should be exceptionally thin or of a serous nature, a drop or two of Mayer's egg albumin may be placed on the slide to make the cells cohere. Frequently, in the normal postmenopausal smear the secretions are scanty and the cells few in number.

A technique for rapid wet-smear staining, of use only in the evaluation of ovarian function, has been described by Rakoff (7). By this technique the smear is collected with a cotton-tipped applicator, which is then placed in a test tube containing approximately 2.5 cc. of normal saline. To the test tube is added 3 drops of the following solution: 10 per cent aqueous solution of Light Green (83 cc.) and 1 per cent aqueous solution of Eosin Y (17 cc.). With this stain the basophilic cells appear green, the eosinophilic cells pink, and cells of intermediate reaction are lavender. Nuclear staining, however, is not exact enough to aid in cancer diagnosis. Nevertheless, this method is a rapid one for the determination of ovarian function, and has a place in clinic and office practice. One can also get some idea of the estrogenic effect by an ordinary wet smear, but because of the staining reaction the foregoing method seems to us to be preferable. Mack's method of staining with iodine vapor (8) can also be used for estrogen effect determination, the more superficial and more cornified cells staining a rich brown.

Interpretation

It is self-evident that the cytologist can base his findings and opinions only on the material given him; consequently, it is necessary that he be presented with as

fair a sampling of the genital secretions as is possible. This is the main reason why we favor at least three smears, as mentioned previously. It is fortunate in some respects that it is in the early stage of carcinoma, when positive findings in the cytology smear may precede clinical symptoms or signs, that well-defined carcinoma cells are found; in the later stages of the disease, necrosis and inflammation increase degenerative changes in the cells being sought.

The cytologist who reads the slide must be a specially trained one, and it takes many months of reading normal as well as abnormal slides before average proficiency is attained. The usual method is to scan the slide first with low power, searching for darkly staining cells and then to scrutinize these cells carefully under high power. Each smear should be looked over systematically.

In general the Papanicolaou smear can be of aid in demonstrating the following: 1) abnormal malignant cells, 2) abnormal "pre-malignant" cells, 3) abnormal non-malignant cells, 4) estrogenic activity, 5) effects of irradiation, 6) infections (such as Trichomonas vaginalis and Monilia albicans), 7) bleeding, and 8) both normal and abnormal cells from sources outside the genital tract.

There are no absolute criteria to enable one to make an unqualified diagnosis of malignancy. Instead, such a conclusion must be based upon a consideration of many changes. Nuclear abnormalities, however, are the mainstays of diagnosis. These may consist of increase and variation in size, fragmentation, hyperchromasia, irregularity of chromatin network and increase in size and prominence of the nucleolus. Cytoplasmic changes are usually less pronounced and significant but comprise variation in the size of the cell, with relatively less cytoplasm than in the normal cell. Many bizarre shapes are found. Vacuolization and degeneration may occur. In carcinoma, too, red cells, white cells, histiocytes and giant cells are often prominent. In our laboratory the slides are classified as "negative," "doubtful," "suspicious" or "positive." This varies from Papanicolaou's system of grading from "one" to "five." Close cooperation and liaison of the clinician with the cytologist is desirable, for in that fashion each learns from the other; mistakes are corrected and impressions are formed.

Benign lesions such as endometrial hyperplasia, polypi and even cervical erosions tend to desquamate, and may account for the presence of cells that would ordinarily be absent in the older woman. These cells are sometimes sufficiently abnormal to be confused with carcinoma. Histiocytes also may be misleading. On the other hand, a questionable slide is still beneficial, in the sense that it stimulates further study of a given case. If, in a woman with severe atrophic changes, the smear is obscured with much debris, it is occasionally advisable to "clear" the smear by local estrogenic therapy.

It is the presence of a moderate to marked estrogenic effect that requires explanation in the smear of the woman over 50 years of age. Such a picture may be the result of endogenous estrogen of adrenal or ovarian origin, but the patient should be questioned about oral and parenteral estrogenic medication, and such conditions as granulosa-cell or theca-cell tumor of the ovary should be considered.

The role of hepatic damage with lessening of estrogen catabolism and consequent hyperestrogenism is still unsettled (9, 10). Preliminary observations in

our clinic indicate that estrogen tolerance is normal in most patients with endometrial carcinoma (11).

An important use of the vaginal smear has been stressed by Graham (12), namely, in the follow-up examination of patients formerly treated for uterine cancer, particularly after therapy by irradiation. Radiosensitivity can be determined by studying the response of the normal vaginal epithelial cells, which are more abundant than the abnormal, even though both undergo changes. In addition, the appearance of new cells suggestive of malignancy following a period of apparent neoplastic inactivity, may precede by weeks or even months any clinical evidence of recurrence.

On occasion, the cytologist is perplexed by cells which arise outside the genital tract. These cells can be explained on the basis of spread from a nearby lesion, *e. g.*, rectal carcinoma, or a fistulous tract.

Relation to other diagnostic tests

The definitive role of the vaginal smear in the diagnosis of genital cancer is in a state of flux. Nevertheless, we believe it safe to say that as more laboratories become acquainted with this method, it will become increasingly apparent that it has great usefulness in the early case which would otherwise go undetected by the history or physical findings, and occasionally even by biopsy. Compared with biopsy at least, it is a simple, painless way of obtaining cells for study.

Yet we do not feel that the problem is exactly one of smear "versus" biopsy, since one method complements the other (13). We believe that a positive *histologic* diagnosis is necessary for proper treatment; although the smear may strongly indicate a certain type of malignancy, it cannot pinpoint the site of the growth. Therefore, treatment on the basis of the smear alone would be dangerous indeed. A good example of this is the finding of adenocarcinomatous cells, the origin of which might be endocervical, endometrial, tubal or even ovarian. Although it may be the first indication of an early lesion, the abnormal smear should lead to biopsy and/or curettage for eventual explanation. One should also remember that negative smears, especially in advanced carcinoma, are not unusual, for the reasons previously mentioned. In our opinion (14) the preferable way to obtain a biopsy specimen in early cervical lesions is by the circular method; and the preferable type of curettage is by the so-called fractional method.

The sponge biopsy has also been used in uterine cancer diagnosis (15). According to Rich (16), it is not as accurate a method as the smear. We personally have not been too impressed by its value. Colposcopy has been used very infrequently in this country but, according to others (17), it also falls short of the smear method.

Value of the smear in the various types of genital malignancy

Uterine cervix. It is in the early diagnosis of beginning cervical carcinoma that the smear has been of outstanding value. In these cases, false negative findings usually fall between 10 and 15 per cent in the average laboratory. The cells may be differentiated or undifferentiated, the basis for this distinction being the

presence of cytoplasm and the outline of cell borders; both of these characteristics are poorly defined in the undifferentiated cell. Fiber cells and tadpole cells are more notable examples of the differentiated variety.

Some authors (18–20) have claimed that carcinoma *in situ* has an almost characteristic smear, and that in such a case one finds superficial dyskaryosis and abnormal parabasal cells. In the last analysis, however, the diagnosis of an *in situ* lesion is histologic, made after examination of many sections. Making such a diagnosis from smears is a form of academic guessing. Trichomonas vaginalis infestation may produce similar changes, as may pregnancy—which is not pertinent to a discussion of geriatric problems.

Uterine corpus. Cells desquamated by endometrial carcinoma show less variation than do those desquamated by squamous-cell carcinoma (21). The incidence of false negative findings, therefore, is about 20 to 30 per cent. Nor is it easy to differentiate endocervical from endometrial malignancy, by smear. In adenocarcinoma the cells may also be differentiated or undifferentiated, and such classifications are based on criteria similar to those of the squamous cell. In the main, such cells tend to occur in groups; vacuolization and leukocytic infiltration are often seen. In adenoacanthoma, adenocarcinomatous and/or malignant squamous cells are found.

With marked endometrial hyperplasia, the ingenuity of the cytologist may be severely taxed to label a given smear benign or malignant. Whether or not the smear in endometrial carcinoma tends to show more estrogen effect than would be expected for the patient's age group, is still under discussion.

Ovaries. If Papanicolaou smears frequently showed positive findings in early ovarian carcinoma, one of gynecology's major problems would be solved; but unfortunately, this is not so. If ovarian malignancy involves the endometrium secondarily, or if the cells of ascitic fluid seep down through the tubal lumina, one may find small, round adenocarcinomatous cells that will aid the cytologist. This occurs in a modicum of instances; we have seen 3 such cases.

Vulva. It is our general rule that a biopsy specimen should be taken from any vulval lesion that does not heal within about two weeks. Several years ago Carter (22) suggested vulval smears for the diagnosis of vulval malignancy. As one would expect, the accuracy is not as high as with biopsy.

Fallopian tubes. Occasionally one finds abnormal endosalpingeal cells in the cytologic smear. In fact, an early case of a rare tubal lesion, sarcoma, was discovered in the Jefferson laboratory (23). By the use of a cervical cap, MacLean (24) has been able to collect a greater number of cells and thereby diagnose a tubal carcinoma in a clinically unsuspected case without a palpable mass.

Vagina. Secondary vaginal carcinoma is far more common than the primary type and both seem to occur in the older woman. Cytologic smears may, as in the case of carcinoma of the cervix, be of value (23).

COMMENT

How does the foregoing affect the physician in treating the older woman? It is our conviction that the clinician has in the Papanicolaou smear a significant

means of further reducing the number of cancer deaths, by detecting lesions in their incipiency. It does not replace a careful history, a meticulous pelvic examination, biopsy and curettage, but adds to them. It is foolish to advocate routine smears on women over a given age because, in the first place, there are not enough trained individuals to read the slides and, secondly, the total cost would be almost prohibitive. In selected cases, however, it is a valuable diagnostic procedure, which only time will adjust to its proper niche among the various measures for cancer diagnosis.

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THE MANAGEMENT OF URINARY TRACT INFECTIONS IN ELDERLY PATIENTS

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The etiology and pathogenesis of urinary tract infections have been well clarified during the past thirty years. The relative importance of systemic foci of infection is well established, and the recognition of the anatomic reasons for persistent or recurrent bacterial invasions has been made possible by improved and well standardized diagnostic techniques.

Instrumental and surgical procedures for the improvement of urinary tract drainage and function have gradually become much more useful and effective (Tables 1 and 2).

Obstructive uropathy as an underlying factor in the cause of recurrent or persistent infections is most common in the very young or in the older age groups. Bacterial invasion will be found associated with obstructive lesions in from 75 to 85 per cent of the older patients presenting themselves clinically.

Prostatic or urethral lesions are the most common causes of obstructive uropathy in older men. Any man past 60 years of age, in whom an inguinal hernia or troublesome hemorrhoids suddenly develop, should be suspected of having an enlarged or malignant prostate or a stricture of the urethra.

Chronic prostatitis and seminal vesiculitis in older men may be responsible for repeatedly converting a dormant urinary tract infection into an active one. Once bacterial invasion has complicated these obstructive lesions it is frequently impossible to eliminate the organisms permanently until the bladder has been made to empty completely.

Compared to twenty years ago, the neurogenic bladder is now less frequently found to be the cause of infected residual urine. This is mainly due to the marked decrease in the incidence of tabes dorsalis in this country during the past thirty years.

In women past middle age, the anatomic changes subsequent to endocrine deficiencies and the trauma of childbirth are common causes of urethral narrowing, relaxation of the pelvic floor and uterine prolapse. These conditions are often accompanied by residual urine which sooner or later becomes infected. Paraurethral gland infections commonly cause repeated re-infections of the bladder. In older women, bladder neck obstructions may develop which are clinically comparable to prostatism in the male. Transurethral resection of obstructing tissue at the bladder neck, and dilatation of the female urethra, are frequently necessary in order to remove the lower tract focus of re-infection.

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In every recurrent or persistent urinary tract infection, a complete urologic study is advisable before continuing with a long and often futile course of urinary antisepsis.

The progress of chemotherapy in the treatment of urinary tract infections during the past fifteen years seems little short of miraculous. Because of these more efficient urinary antiseptics, we are now able to cure many older patients permanently of their urologic lesions by surgical and manipulative measures. Many of these patients previously died because we had no adequate means of controlling the local infections.

TABLE 1

Treatment of Urinary Infections, Chronic or Recurrent

Search for and elimination of foci of infection.
Urologic examination to determine existence of obstructive lesions, calculi, tumors, anomalies.
Chemotherapy.
Surgical, transurethral or manipulative treatment.

TABLE 2

Treatment of Acute Urinary Infection

Bed rest
Proper diet
Detoxication of patient
Intestinal cleansing
Adequate fluid intake:
by mouth
hypodermoclysis (hyaluronidase)
intravenously
proctoclysis
Electrolytic balance:
watch blood sugar, chlorides, K and Na
combat acidosis CO_2
To this management may be added suitable chemotherapy

In the light of our present knowledge, the bacteriology of urinary invasions has become increasingly important. The clinician of today should have available not only a means of accurately identifying the organisms present in the urine, but also the means of determining which drugs are specific in destroying the various strains *in vitro*. Here, as well as in the clinical examinations, team-work plays an important role in making the best clinical progress toward applying the advancing knowledge of chemotherapy.

The present availability of sulfonamides of improved urinary solubility, and of the broad-spectrum antibiotics potent against a wide range of gram-negative and gram-positive micro-organisms, has greatly changed the outlook for older persons suffering from urinary tract infections.

Prompt and vigorous treatment with properly chosen antibacterial agents will

materially shorten the febrile period, ameliorate the distressing systemic symptoms of acute episodes of pyelonephritis and reduce pyuria dramatically. However, abundant experience has shown that now, as in the past, if the obstructive lesions responsible for the infection in the first place are not corrected, no permanent relief will be obtained. Moreover, elderly persons present certain other special problems which must be dealt with, as will be pointed out later.

In a series of 325 patients of all ages with urinary tract infections which we studied, obstructive lesions of some type were discovered in 75 per cent. Although there was evidence of pathologic changes in both the lower and upper urinary tract in a great many of the patients, the most obvious anatomic involvement was 1) in the urethra or bladder in roughly two thirds of the patients and 2) in the ureters, kidney pelves, and kidney parenchyma in the remainder. When pus is found in the urine and physical examination reveals a urethral caruncle, cystourethrocele or a large prostate, many of us jump to the conclusion that these obvious lesions are the sole cause of the patient's urinary tract infection. Such facts as have been pointed out previously make it clear that these assumptions are unwarranted. Unless the infections in question are of a very minor and transient nature, these patients should, in addition, have cystoscopy and roentgen visualization of the entire urinary tract. We have already discussed the various lesions that such examinations most commonly disclose in elderly subjects. The correction of these anatomic irregularities lies within the urologist's field.

However, the internist and general practitioner also have special responsibilities in management. First, the causative organism must be identified by cultures of the catheterized urine. No longer is it defensible to assume that one is dealing with a colon bacillus infection until proven otherwise, and to give urinary antiseptics in a hit-or-miss fashion. Indeed, in our series, the colon bacillus was the responsible organism in slightly less than half the cases. The organisms most frequently encountered are listed in Table 2.

It will be noted that Pseudomonas aeruginosa, for instance, is found much more frequently in upper urinary tract infections than in lower. In our experience, it is present chiefly when kidney stones, tumors and strictures are the obstructing lesions and when extensive instrumentation has been necessary. Such lesions are, of course, much more common in older patients than in those below the age of 50. Also, two or more organisms are frequently found growing together—especially E. coli and Streptococcus fecalis—in the original culture. Often, as one micro-organism disappears under therapy, another is found to have taken its place when subsequent cultures are made.

From these findings, it is clear that the antibiotic or chemotherapeutic agent, or the combination of them, to be used in a given infection must be chosen with care for the particular problem at hand. Our suggestions, arrived at on the basis of therapeutic results as well as *in vitro* tests of sensitivity, appear in Tables 3–9. It is important that full doses of the antibiotics be used as indicated, that treatment be continued at least one week, and that recultures of catheterized urine be made at least forty-eight hours after therapy has been terminated, in

TABLE 3

Micro-organisms Responsible for Urinary Tract Infections—325 Cases

E. coli	46.4
Streptococcus fecalis	21.2
Pseudomonas aeruginosa	14.0
Aerobactor aerogenes	3.0
B. proteus	4.0
Staphylococcus albus and aureus	6.0
K. pneumoniae	1.5
N. tuberculosis	1.5
M. tetragenus	1.5
Streptococcus hemolyticus	0.6
B. subtilis	0.6

Multiple micro-organisms in original cultures: 63 cases.
Change in bacterial flora of urine of patients: 74 cases.

TABLE 4

Choice of Antibacterial Agents in Urinary Tract Infections

Organism	Aureo	Terra	Chloro	Dihydro-strep.	Penicillin	Polymy.*	Gantrisin	Mandel
Minimum daily dose Minimum duration	2 Gm. 7 days	2 Gm. 7 days	2 Gm. 7 days	1–2 Gm. 7 days	800,000 u 7 days	150–200 mg. 7 days	G6–9 Gm. 10 days	8 Gm. 10 days
E. coli	1	1	1	2	—	—	2	3
Strep. fecalis	1	1	1	2	2	—	3	3
Ps. aeruginosa	3	2	—	2	—	1	2	
B. proteus	3	—	1	2	2		1	
A. aerogenes	3	2	2	2		1	2	
K. pneumoniae	2	2	2	2		1		
Staphylococcus	1	1	3		2		3	
Strep. hemolyticus	2	2			1		2	

1 = 1st choice; 2 = 2nd choice; 3 = 3rd choice.
* Toxic reactions more common than with other antibiotics.

TABLE 5

E. coli

	% of strains completely inhibited by <25 mcg./ml.
Aureomycin	61
Chloramphenicol	57
Terramycin	45
Aerosporin (Polymyxin B)	38
Streptomycin	33
Penicillin	6
Combinations more effective than single agents:	
Aureomycin + Streptomycin	85
Aureomycin + Chloramphenicol	84
Aureomycin + Aerosporin	79
Streptomycin + Terramycin	62

order to be sure that the responsible micro-organism has been eradicated. In our series studied in this way, 53 per cent of the patients with no evidence of obstructive lesions in the urinary tract had negative results from recultures. In only 7.6 per cent in whom an obstructing lesion was demonstrated was the infection permanently controlled. In every one of the latter instances, it was necessary

TABLE 6

Streptococcus fecalis

	% of strains completely inhibited by <25 mcg./ml.
Aureomycin	61
Chloramphenicol	53
Streptomycin	47
Terramycin	40
Aerosporin (Polymyxin B)	36
Penicillin	12
Combinations more effective than single agents:	
Streptomycin + Aureomycin	83
Aureomycin + Chloramphenicol	72
Aureomycin + Aerosporin	65
Streptomycin + Terramycin	64

TABLE 7

Pseudomonas aeruginosa

	% of strains completely inhibited by <25 mcg./ml.
Aureomycin	20
Terramycin	16
Chloramphenicol	12
Aerosporin (Polymyxin B)	9
Streptomycin	4
Penicillin	4
Combinations more effective than single agents:	
Aerosporin + Streptomycin	64
Aerosporin + Aureomycin	64
Streptomycin + Terramycin	48
Aureomycin + Gantrisin	48
Aerosporin + Chloramphenicol	46

to eliminate the obstructing lesion before permanent sterilization of the urine was effected.

In addition to sharing the responsibility for antibacterial therapy, the internist or family physician must help in evaluation of the elderly patient as a surgical risk in those instances in which operation of some type becomes necessary.

Diabetes must be recognized and brought under control, whether or not surgery is required. The cardiac status must be carefully evaluated. In our experience, auricular fibrillation, cardiac enlargement and valvular insufficiency do not

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Diabetes must be recognized and brought under control, whether or not surgery is required. The cardiac status must be carefully evaluated. In our experience, auricular fibrillation, cardiac enlargement and valvular insufficiency do not

often, in themselves, constitute a contraindication to surgery, if the patient's heart is not decompensated. Decompensation does present a definite hazard and should, if possible, be corrected before any instrumentation is undertaken.

Many older patients with urinary tract infections are badly dehydrated, with resultant azotemia and acidosis. The importance of correcting this water deficit by giving fluids (by mouth, if possible; but by vein, if necessary) cannot be stressed too much. The composition of the fluids to be given must be dependent upon electrolyte studies of the blood and urine. Usually 5 per cent glucose in

TABLE 8

Aerobactor aerogenes

	% of strains completely inhibited by <25 mcg./ml.
Aureomycin	57
Chloramphenicol	43
Aerosporin (Polymyxin B)	29
Terramycin	29
Combinations more effective than single agents:	
Streptomycin + Aureomycin	86
Aerosporin + Aureomycin	86
Chloramphenicol + Terramycin	71
Chloramphenicol + Aureomycin	71
Chloramphenicol + Aerosporin	57

TABLE 9

Aerosporin (Polymyxin B)

Most effective in Pseudomonas aeruginosa

B. pyocyaneus

Commonly found in urinary tract after instrumentation, catheter, or open surgical procedures.

Topical: 1 % in sterile saline for instillation or irrigation in bladder or renal pelvis.

Parenteral: 50 mg. intramuscularly every 6 to 8 hours for 3 to 4 days. Additional 3 days of 25 mg. every 8 hours.

As lubricant for catheter or sound: Polysporin brand Polymyxin B-Bacitracin Ointment

water is safe but, in cases of chloride or salt depletion, physiologic solution of sodium chloride may be indicated. In cases of advanced acidosis, ⅙ molar sodium lactate solution may be required.

We are constantly amazed at the manner in which older individuals with advanced arteriosclerosis and/or hypertension withstand urologic procedures. However, special precautions must be taken to avoid shock in such persons. The physiologic mechanisms for adjusting to changes in blood volume are not working at optimum efficiency. If there is considerable blood loss, for example, following transurethral resection, this loss must be recognized and replaced promptly if serious permanent changes are to be avoided. For the same reason,

older individuals whose red blood cell counts are below 3,500,000 should have blood transfusions prior to operation.

Sudden drops in blood pressure in elderly patients may result in cerebral or coronary thrombosis or renal shut-down, and are to be avoided if at all possible. For this reason, the addition of pressor substances, such as neosynephrine or arterenol to spinal anesthetics is usually indicated.

Early ambulation of elderly patients, especially following prostatectomy or repair of cystourethrocele, is of paramount importance in avoiding thromboses in the veins of the legs which, in the past, so frequently resulted in pulmonary embolism. If these patients can be out of bed within forty-eight hours after their surgery, anticoagulant therapy usually can be avoided. This is important, because operative procedures in the urinary tract often result in minor bleeding for several days, and this hemorrhage may assume serious proportions if blood coagulation is interfered with.

CONCLUSIONS

The management of urinary tract infections in older patients, by the use of modern chemotherapeutic agents, has brought about a spectacular improvement in mortality and morbidity rates during the last five years.

Clinical observations and laboratory findings must be correlated in the proper application of these newer chemotherapeutic agents.

In the care of these older patients, male or female, the combined efforts of the internist on the one hand, and the urologist on the other, are most important in obtaining the greatest benefit for the patient.

Current Geriatric Literature

THE EXPERIENCE OF A GROUP INSURANCE PLAN WITH OLDER ENROLLEES.
G. Baehr and N. R. Deardorff.
J. Gerontol. **7:** 245, 1952.

The utilization of the services of the Health Insurance Plan by 50,251 enrollees over the age of 50 is compared with that of 224,314 younger enrollees during 1948–1949. The data demonstrate that the older employed persons are not inordinate users of physicians' services. Those supported by public agencies not enrolled in the plan constitute a peculiar medical care problem. Their inclusion would require a modification of this statement. It is not believed that under group enrollment the inclusion of the employed aged in a prepaid medical care plan would materially affect the premiums. This refers to the premium rates necessary for good medical care of families at other stages of their life cycle. It would require that the older persons be enrolled in the proportion in which they exist in the general population.

The aging group is still a relatively small fraction of the population (it will be about 13 per cent by the year 2000). There is, therefore, no justification for excluding the aged from participation in community plans for prepaid medical care.

ACUTE APPENDICITIS IN CHRONICALLY ILL GERIATRIC PATIENTS.
L. Carpaud and J. A. Armino.
Am. J. Surg. **83:** 773, 1952.

Although of comparatively low incidence among elderly patients, acute appendicitis is usually serious. Thirteen male patients aged 60–90 were observed. An atypical clinical syndrome, difficulty in diagnosis, delayed operation, catharsis and degenerative disease contribute to high mortality, which was found to be 23.8 per cent. Peritonitis, pneumonia, cardiac failure and thrombosis have been the leading causes of fatalities. The death rates might be reduced by: 1) Early diagnosis through better education of the public. 2) Quick intervention after supportive therapy, with appendectomy as a routine procedure. It is preferable to tie off the appendix at its base, amputate it and phenolize the stump without inversion, particularly if time and an over-edematous and friable cecum are factors. 3) Drainage, in cases of peritonitis or abscess. 4) Use of McBurney incision, unless exploratory celiotomy is indicated because of doubtful diagnosis. 5) Interdiction of abdominal closure above the peritoneum or fascia, if contamination has occurred. 6) Carefully chosen, expertly administered anesthetic. 7) New supportive and antibiotic therapy. 8) Early ambulation. Sulfonamide and antibiotic therapy has reduced the mortality. Blood transfusions, maintenance of adequate chemical balance and gastrointestinal tube decompression are of great importance.

Sometimes observations suggest that early massive gangrene results from diminution of lymphoid follicles in the appendix wall.

TESTOSTERONE AND POSTOPERATIVE LIVER DAMAGE.
A. M. Hayes, P. E. Hodgson and F. A. Coller.
Ann. Surg. **136:** 643, 1952.

The danger of the liver being damaged by volatile anesthetics has been appreciated since their early days. Before anything was known about the factors affecting hepatic susceptibility to exogenous toxins, little could be done to prevent this damage. However it is now established, that depletion of hepatic stores of protein and glycogen increases this susceptibility.

Postoperative recovery of patients so depleted may be improved by inducing positive nitrogen balance before operation. However, difficulties may arise in ensuring a suitable

diet, especially orally, for several reasons. Therefore the anabolic effects of steroid hormones, especially testosterone, have proved valuable in such cases. There is a discussion of the treatment of 8 patients, aged 69 to 78, suffering from esophageal or gastric neoplasms preventing feeding by mouth. Daily intramuscular injections of 50 mg. of testosterone propionate were given to several of them for seven days. The rest served as controls.

Also a standard subcutaneous injection of adrenaline was made as a measure of hepatic glycogen reserve. Definite improvement was produced by parenteral feeding. Further increase in response to epinephrine followed doses of testosterone.

The foregoing shows that the anabolic effects of testosterone are of great value in preoperative reinforcement of hepatic resistance. Simultaneous increase in blood volume and plasma protein considerably reduce subsequent risk of shock. However, testosterone may reduce the sensitivity of the pituitary to stress and interfere with steroid homeostasis. This can be controlled by intravenous administration of aqueous cortical extract.

WHAT NEEDS TO BE DONE IN HIGH BLOOD PRESSURE RESEARCH.
L. N. Katz.
Acta med. Scandinav. suppl. 266: 623, 1952.

The needs of research in the problem of high blood pressure are many. The most important is the task of advancing the borders of our present knowledge. Our primary concern should be to discover the fundamental cause of high blood pressure. This is, of course, closely related to hardening of the arteries; it may lead to heart failure, coronary disease or kidney failure, even to apoplexy. Thrombosis is one of the more frequent complications. Cardiovascular diseases should be considered as different facets of one generic disturbance. It must be recognized that a discovery relating to one of the cardiovascular disorders has important implications for all of the others. Through Goldblatt's method of producing chronic experimental high blood pressure, some progress was achieved. This involved interference with some function of the kidney. However, there is need to pursue further the fundamental problem of the cause of high blood pressure along other lines. Especially the role of the various endocrine glands and their hormones must be considered more thoroughly. The nervous system also comes decidedly into consideration. Our pace of living, and civilization with its emotional impacts, frustrations and stresses open the way to high blood pressure. These factors either act as trigger mechanisms, or else in a more fundamental, but still unknown manner. The reactions of the blood vessels must be studied more thoroughly. Their alteration is recognized to be primarily responsible for any elevation of the blood pressure. Basic research, even disciplines more or less closely related to medical science, are of greatest importance. We should not only concentrate upon the problem of high blood pressure and its manifestations; an even broader vision is required. One should go farther afield into biology, physics, chemistry and sociology. We should be seeking help from leads in those disciplines. They may open the pathway to the solution of the problem of high blood pressure.

CHANGES OF THE PERIODONTAL TISSUE IN OLD AGE. (Veränderungen des periodontalen Gewebes im Alter.)
St. Loos.
Wien. klin. Wchnschr. **64:** 999, 1952.

Typical changes of the periodontal tissue in aged individuals are discussed. They refer principally to increasing shortening of the clinical alveoli dentales. Lengthening of the clinical crowns is also a typical symptom in old people. This finally leads to loss of the teeth involved.

Manifestations of the process of senile involution in the bony tissue mostly consist of increasing rarefaction of the spongiosa. Another item of this process is loosening of the compacta. In the foregoing changes, calcification of the fibers of the periodontal membrane (dental periosteum) in old age plays an important rôle. Amorphous deposits of lime and formations of cementicles in the periodontal membrane of a tooth (cemento-exostosis) are caused thereby.

Differentiation between senile processes of this type and other phenomena occurring in younger patients, is discussed. The last mentioned changes are produced by periodontal diseases showing similar symptoms. Therapeutic suggestions are made for treatment of the necks of teeth which, in old individuals, are frequently exposed and hypersensitive.

RECONSTRUCTIVE SURGERY FOR THE ELDERLY.

A. P. Seltzer.

Geriatrics **7**: 185, 1952.

Among a large number of persons, aging is first apparent in the skin. The loss of skin elasticity means lack of ability of the tissues to maintain their earlier optimum water content. This invariably leads first to furrowing of the skin. Later, progressive loss of muscle tone is involved. Any physical distortion or deformity is recognized as an emotional irritant. Therefore, the desirability of correction by reconstructive surgery is freely granted. Naturally the operation has to be carried out with all the precautions for major surgery. Anesthetization is of special concern. It has often been said that the anesthetic is of less importance than the anesthetist. This is especially true in operating on older people. The greatest accuracy can be secured by marking the desired line of the incision on the skin. This preliminary step should preferably be made within the hairline, in order to conceal any possible resulting scar. Beginning above, the incision follows the pattern of the hairline to the point where the ear is attached. Then it follows carefully along the front outline of the ear, curving around the lower attachment of the ear. Finally it should be carried across behind the ear to the postaural hairline. If there is much sagging of the skin of the neck, this last segment of the incision should extend across to the occipital hairline. In order to avoid unnecessary postoperative skin retraction, all parts of the incision should be made to correspond with Langer's lines. The degree of permanence of the operation depends to a large extent upon the undermining of the skin. There is no arbitrary rule for carrying out the undermining. However, in general it should depend upon the amount of skin to be removed. It also depends upon the elasticity of the skin concerned. After forty-eight hours the drains are removed. All sutures are removed on the fourth or fifth day.

EFFECT OF OMITTING BREAKFAST ON THE PHYSIOLOGIC RESPONSE OF THE AGED.

W. W. Tuttle, K. Daum, C. J. Imig, B. Randall and M. T. Schumacher.

J. Am. Dietet. A. **28**: 117, 1952.

Data from 8 men, aged 60 to 83, were collected showing the effect of omission of breakfast.

The items of investigation were as follows: choice reaction time, neuromuscular tremor magnitude, maximum grip strength, strength endurance, and oxygen required in performing uniformly specified amounts of exercise.

a) Choice reaction time was not affected, excepting in 1 subject. He had a consistently longer reaction time during the "no breakfast" period.

b) Breakfast omission resulted in increased neuromuscular tremor magnitude in the majority of cases.

c) Maximum grip strength became less in the majority of cases, when the morning meal was omitted.

d) Omission of breakfast resulted in a decrease in strength endurance in the majority.

e) One half of the subjects required more oxygen to walk on a treadmill up a 2 per cent grade. This was at the rate of 2 miles per hour for three minutes after omitting breakfast.

f) The type of breakfast did not affect significantly the physiologic response of this group of older men.

THE 1953 MEETING OF THE AMERICAN GERIATRICS SOCIETY

The 10th Annual Meeting of the American Geriatrics Society will be held at the Hotel Commodore in New York City, May 28–30, 1953.

All members who plan to attend the meeting should reserve accommodations at the Hotel Commodore at once. The meeting is being held just before that of the American Medical Association and the hotels expect to be filled to capacity. The program is probably the most interesting one that has been arranged for the Society up to the present time.

The Annual Dinner of the Society will be held on Friday evening, May 29, at 7:30 preceded by cocktails at 7:00. Wives and guests of members are welcome.

The Annual Business Meeting will be held Thursday, May 28.

PRELIMINARY PROGRAM

HOTEL COMMODORE

THURSDAY, MAY 28, 1953

8:00 A.M. **Registration** (*South Room*)
9:00 A.M. **Annual Business Meeting** (*South Room*)
2:00 P.M. **General Session** (*West End Ballroom*)

Harold W. Lovell, M.D., *Presiding*

1. Aging Skin
   Eugene F. Traub, M.D., New York, N. Y.
2. Functional Digestive Disease in the Aged
   Sara M. Jordan, M.D., Boston, Mass.
3. Common Blood Problems in Older People
   Paul Reznikoff, M.D., New York, N. Y.
4. Old Age and the Vices
   Russell L. Cecil, M.D., New York, N. Y.

Walter E. Vest, M.D., *Presiding*

5. Bronchial Asthma and Pulmonary Emphysema
   Alvan L. Barach, M.D., New York, N. Y.
6. The Coronary Problem in Relation to Aging
   Robert L. Levy, M.D., New York, N. Y.
7. Clinical Diagnosis of Atherosclerosis of the Coronary Arteries
   Robert E. Mason, M.D., Baltimore, Md.
8. The Heart and Arteries in Mid-Life
   Teofil Kheim, M.D., and William B. Kountz, M.D., St. Louis, Mo.

FRIDAY, MAY 29, 1953

8:00 A.M. **Registration** (*South Room*)
9:00 A.M. **General Session** (*West End Ballroom*)

Cortez F. Enloe, *Presiding*

9. Psycho-Physical Compensatory Adjustments in the Aged
   Edward B. Allen, M.D., and Hollis E. Clow, M.D., White Plains, N. Y.
10. Alcoholism in Geriatric Practice
   Harold W. Lovell, M.D., and John W. Tintera, M.D., New York, N. Y.
11. The Effect of Aging and Arteriosclerotic Cerebral Vascular Disease on the Circulation and Metabolism of the Brain
   Albert Heyman, M.D., and John L. Patterson, Jr., M.D., Atlanta, Ga.
12. Relation of Physiologic Aging to Physical Medicine
   Malford W. Thewlis, M.D., Wakefield, R. I.

Edward Henderson, M.D., *Presiding*

13. A Realistic Approach to Rehabilitation in Geriatrics
   Samuel G. Feuer, M.D., New York, N. Y.
14. Medical Rehabilitation and De-Aging Methods
   C. Ward Crampton, M.D., New York, N. Y.

Panel Discussion

THE INSURANCE COMPANIES AND THE AGING POPULATION

C. L. Reeder, M.D., Moderator

15. Life Insurance
   Howard B. Brown, M.D., Medical Director, Massachusetts Mutual Life Insurance Company, Springfield, Mass.
16. Plan for Retirement
   Paul V. Reinartz, M.D., Associate Medical Director, The Prudential Insurance Company of America, Newark, N. J.
17. Hospitalization Insurance
   C. L. Reeder, M.D., Medical Director, Continental Assurance Company, Chicago, Ill.
18. Disability Insurance
   Harold R. Leffingwell, M.D., Medical Director, Paul Revere Life Insurance Company, Worcester, Mass.

General Discussion

INTERMISSION FOR LUNCH

2:00 P.M. General Session (*West End Ballroom*)

Caesar Portes, M.D., *Presiding*

19. Diabetes in the Elderly
   Alexander Marble, M.D., and Emery C. Miller, M.D., Boston, Mass.
20. Pathology of Myxedema in the Aged
   Prof. Paul Bastenie, Brussels, Belgium
21. Calcium Metabolism in the Aged
   Herta Spencer, M.D., New York, N. Y.
22. The Effects of Androgenic Steroids in Aging Individuals
   Jonas Weissberg, M.D., Sidney Pearson, Ph.D., and T. H. McGavack, M.D., New York, N. Y.

Russell L. Cecil, M.D., *Presiding*

23. Geriatric Gynecology at the New York Hospital
   Ralph W. Gause, M.D., New York. N. Y.
24. Diagnosis and Treatment of Cancer of the Breast in Older Patients
   Louis P. River, M.D., Chicago, Ill.
25. The Management of Prostatism in the Aged
   Norris J. Heckel, M.D., Chicago, Ill.

26. Treatment of Common Anorectal Diseases in the Aged
Caesar Portes, M.D., Chicago, Ill.
27. Indications for Eye Surgery: The Physiological Bases
Arthur Alexander Knapp, M.D., New York, N. Y.

ANNUAL DINNER, Friday, May 29, 1953

West End Ballroom

7:00 P.M. Cocktails

7:30 P.M. Dinner

Geriatrics Comes of Age—Willard O. Thompson, M.D., *Toastmaster*

Magic—Malford W. Thewlis, M.D.

SATURDAY, MAY 30, 1953

8:00 A.M. Registration (*South Room*)

9:00 A.M. General Session (*West End Ballroom*)

Thomas H. McGavack, M.D., *Presiding*

28. The Diagnosis and Management of Acute Pancreatitis in Geriatric Patients
Brock E. Brush, M.D., Ralph Carlson, M.D., and Fred Zeller, M.D., Detroit, Mich.
29. Hiatus Hernia—A Geriatric Problem
Edward Henderson, M.D., Bloomfield, N. J.
30. Abdominal Surgery in the Aged Patient
E. Lee Strohl, M.D., Chicago, Ill.
31. The Surgical Treatment of Non-Malignant Disease of the Biliary Tract in Patients 65 Years of Age and Older
Frank Glenn, M.D., and Daniel M. Hays, M.D., New York, N. Y.
32. Diagnosis and Treatment of Cancer of the Head and Neck
John J. Conley, M.D., New York, N. Y.

Alfred H. Iason, M.D., *Presiding*

33. Postoperative Mortality in the Aged
Max S. Sadove, M.D., and Myron J. Levin, M.D., Chicago, Ill.

Symposium on Fractures of the Hip Joint

34. Management to Improve Longevity in Patients with Fractured Hip
Julian A. Sterling, M.D., and Ralph Goldsmith, M.D., Philadelphia, Pa.
35. Restitutive Surgery of the Hip Joint and its Evolution
Stephen S. Hudack, M.D., Kent L. Brown, M.D., and Robert Cooke, M.D., Cleveland, Ohio
36. Rationale of Immediate Fixation of Fractures about the Hip in Elderly Patients
David M. Bosworth, M.D., New York, N. Y.

INTERMISSION FOR LUNCH

2:00 P.M.–5:00 P.M. Geriatric Day at the William I. Sirovich Day Center, 201 Second Avenue, New York City. Courtesy of Harry Levine, Founder, and Miss Frances King, Director. Physicians, families and guests are welcome to

see the unusual work that is being done at this center. The dramatic group and the orchestra will perform, and visitors may make a tour of the work shop which includes ceramics, sculpture, art and millinery.

TO BE READ BY TITLE

37. Ultrasonic Therapy in Geriatrics
H. J. Behrend, M.D., New York, N. Y.
38. The Essentials for Rehabilitation in the Aged
James L. Blanton, M.D., Clifton Springs, N. Y.
39. Abdomino-Perineal Resection Beyond the Age of Sixty
J. A. Buckwalter, M.D., and S. E. Ziffren, M.D., Iowa City, Iowa
40. Cicero's "De Senectute." An Analysis
Louis Carp, M.D., New York, N. Y.
41. Studies of the Variations in Human Blood Heparin Levels According to Age, Sex and Atherosclerotic Disease
Hyman Engelberg, M.D., Los Angeles, Calif.
42. The Management of Thyroid Disorders in the Elderly
Bernard J. Ficarra, M.D., Brooklyn, N. Y.
43. The Happy Senile
O. L. Friedman, M.D., New York, N. Y.
44. A Test of Vitality
Martin Gumpert, M.D., New York, N. Y.
45. The Significance of Nasal and Respiratory Physiology in the Aging
Emanuel M. Josephson, M.D., New York, N. Y.
46. Diagnosis and Treatment of Gout: Effects of ACTH in the Acute Attack
Fred Kauffman, M.D., Canton, Ohio
47. Psychotherapy of Neurosis and Psychoses in the Elderly
Hans J. Kleinschmidt, M.D., New York, N. Y.
48. Accelerated Aging
C. M. Longstreth, M.D., and George H. Chapman, M.D., New York, N. Y.
49. D.D.T. in Human Fat
William Coda Martin, M.D., New York, N. Y.
50. The Involutional and Senile Psychoses
James L. McCartney, M.D., Garden City, Long Island, N. Y.
51. Proctologic Problems Past Middle Age
J. F. Montague, M.D., New York, N. Y.
52. Hypophysis Cerebri in Psychosis
James W. Papez, M.D., and B. Pearl Papez, M.D., Columbus, Ohio
53. The Treatment of Pulmonary Emphysema in the Aged
William K. Swann and Thomas L. Lomasney, Knoxville, Tenn.
54. Acute Large Bowel Obstruction in the Elderly Patient
Alex W. Ulin, M.D., Paul J. Grotzinger, M.D., and Phyllis Ostrum, M.D., Philadelphia, Pa.
55. Cancer of the Gall Bladder, A Geriatric Problem
Alex W. Ulin, M.D., Seymour Wagner, M.D., and William L. Martin, M.D., Philadelphia, Pa.
56. The Management of Fractures of the Neck of the Femur in the Aged
S. E. Ziffren, M.D., C. L. Beye, M.D., and M. S. Goldstein, M.D., Iowa City, Iowa

SCIENTIFIC SESSIONS ARE OPEN TO THE MEDICAL PROFESSION AND TO THOSE WHO ARE ESPECIALLY INTERESTED IN THE PROBLEMS OF AGING